Neuromuscular electrical stimulation is effective in maintaining physical capacity during an exacerbation of chronic obstructive pulmonary disease - a pilot study

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Neuromuscular Electrical Stimulation is effective in maintaining physical capacity during an exacerbation of Chronic Obstructive Pulmonary Disease- a pilot study.

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Abstract

Background: Pulmonary rehabilitation for patients with Chronic Obstructive Pulmonary Disease (COPD) traditionally incorporates exercise training. Since COPD is characterised by periods of exacerbation of their disease, at this time patients may be unable to complete any exercise due to breathlessness or peripheral muscle weakness. Neuromuscular Electrical Stimulation (NMES) has been shown to improve the fundamental properties of muscles; therefore it has been hypothesised that NMES of the quadriceps femoris muscles may be able to maintain physical capacity during an exacerbation of COPD.
Methods: A randomised controlled trial was designed. A sample of 20 participants of mean (SD) age 70.5 (9.3)yrs admitted to hospital with an acute exacerbation of COPD (mean (SD) Forced Expiratory Volume in 1 second (FEV_1) 0.82 (0.39) (30.4% predicted) were recruited. The group were randomised into an experimental group who undertook NMES of the quadriceps for 30 minutes each day, and were also encouraged to mobilise until constrained by symptoms; or randomised into a control group who undertook NMES using a 'sham' technique as well as being encouraged to mobilise until constrained by symptoms. Patients participated in the study for 4 weeks. Quadriceps strength, and exercise capacity measured by Incremental Shuttle Walk Test (ISWT) were taken at baseline, on discharge from hospital and at 4 week follow-up. Patients also completed health related quality of life questionnaires, and were asked to wear an activity monitor during their in-patient stay.
Results: There were no significant differences between the baseline measurements. In the experimental group (n=8) over the 4 week trial period there was an overall increase in quadriceps strength of 9.1 (SD 15.5)Nm (95%CI –22.0 to 3.9). The control group (n=5) also demonstrated an increase in quadriceps strength 37.4Nm (SD 104.6) (95%CI -203.9 to 129.0). However neither of these increases were significant $p<0.05$, there were no differences between groups. ISWT performance was also improved in the experimental group, at baseline the mean (SD) distance was 21.0 (n=8) (SD 37.8)m. On discharge from hospital the mean had increased to 61.0 (SD 49.0)m (mean increase 40m) (95%CI –81.2 to1.2). This increase was not significant ($p=0.056$ (df=9), results showed a strong trend towards statistical significance. During the period from discharge to 4 weeks there was a significant increase in ISWT performance $p=0.026$ (df=5). The ISWT in the control group also increased again this was not a significant increase, mean baseline ISWT was 10.0 (n=5) (SD 20.0)m (95%CI –291.7 to 81.7), at discharge the mean distance was 115.0 (SD 109.1)m (mean increase of 105m n=5) and at 4 weeks the mean distance was 100.0 (SD 93.0)m (a mean increase of 90m from baseline to 4 weeks) from baseline to 4 weeks $p=0.106$ (df=4) (CI –214.7 to 30.7). There were no statistically significant improvements in health related quality of life, however there were clinically significant improvements (>0.5 change in score) in the mastery domain of the Chronic Respiratory Questionnaire (CRQ-SR) following NMES.
Conclusion: This study has demonstrated that NMES is feasible during an acute exacerbation of COPD to maintain physical capacity, although it is difficult to draw conclusions from, as the groups were small.

Introduction

The National Institute for Clinical Excellence (NICE) (2004) define Chronic Obstructive Pulmonary Disease (COPD) as a condition characterised by airflow limitation, which is progressive and not fully reversible; it is an umbrella term for what was previously known as Chronic Bronchitis and Emphysema. MacNee (2005) reiterates that chronic airflow limitation results from an inflammatory response to gases within the lungs and inhaled particles, predominantly caused by smoking.

Airflow limitation occurs as a result of airway and paranchymal damage resulting from inflammation due predominantly to tobacco smoking. COPD is characterised by symptoms such as chronic cough and increased sputum production; disability and impaired quality of life (NICE 2004). Ries *et al* (2007) suggest that morbidity from COPD is high because affected individuals remain undiagnosed until their disease is relatively advanced due to the insidious onset of symptoms. It is also well documented that COPD is a major cause of hospital admission, disability, morbidity, and high health care expenditure (Yohannes and Connolly 2004).

The World Health Organisation's (WHO) world health report lists COPD as the fifth most common cause of death worldwide (Celli *et al* 2005). In the United Kingdom (UK) it is reported that COPD accounts for over 90000 admissions to hospital per year, this number has risen over the past 10 years costing approximately £817.5m (Ram *et al* 2004). This translates to a prevalence of

66-69/1000 population (Sillen *et al* 2009). This illustrates the extent the socio-economic burden has extending beyond the individual but also on society.

Diagnosis

NICE (2004) recommend that a diagnosis should be considered if a patient is over the age of 35 and presents with a risk factor, (commonly smoking) who demonstrates breathlessness on exertion, chronic cough, sputum production and winter 'bronchitis' or wheeze.

The severity of airflow limitation should then be determined by pulmonary function tests (spirometry). These tests aim to detect and define abnormal lung function, allow assessment of lung function and to monitor the effect of treatment and progression of the disease (Axford 1996). The test commonly measures both the volume of air expelled in the first second of forced expiration (FEV_1), and the total volume that can be expelled in a single expiration (forced vital capacity FVC). The Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) (2006) define mild COPD as FEV_1/FVC <70% FEV_1≥80% predicted, moderate COPD as FEV_1/FVC <70% 50%≤ FEV_1 80% predicted, severe COPD as FEV_1/FVC <70%, 30%≤ FEV_1 ,50% predicted and very severe COPD as FEV_1/FVC <70%, FEV_1 <30% predicted or FEV_1 <50% predicted plus chronic respiratory failure.

Disease Monitoring

Initial investigations into the progression of COPD incorporate pulmonary function tests. The FEV_1 measurements are a highly predictive factor in the

clinical outcome of COPD exacerbations (Willaert *et al* 2002). Although spirometry has its uses in assessing lung function further research suggests that the assessment of COPD is more complicated and incorporates other factors. Celli *et al* (2005) concur by implying that since COPD has a complex pathophysiology factors other than FEV_1 need to be considered. They proposed a model of evaluation called the BODE index. The four factors identified were Body Mass Index (B), airflow obstruction (O), dyspnoea (D), and exercise capacity (E). This index is able to correlate patients with their prognosis; the BODE index scoring is predictive not only for death from respiratory causes but also from any other cause; scoring by quartiles is also more predictive than scoring by spirometry alone (Celli *et al* 2005).

This is a comprehensive model as it incorporates not only the pulmonary aspects of the condition but also the systemic effects. This is illustrated by Eisner *et al* (2007) who note that low Body Mass Index (BMI) is associated with higher mortality in COPD and functional limitation; however they also found that a higher fat mass had a negative effect on function.

Exacerbation

COPD is a disease punctuated by periods of exacerbation. NICE (2003) define an exacerbation as,

> "A sustained worsening of the patients' condition from their usual stable state, and is acute in onset." (NICE 2003).

Willaert *et al* (2002) expand on this definition by stating that an exacerbation is characterised by increased dyspnoea, increased cough frequency or

severity, an increase in sputum production or purulence and increased wheeze.

Man *et al* (2004) illustrate the relevance of exacerbation by stating that over the past decade admissions to hospital for acute exacerbations of COPD have increased by 50% in the UK. Acute exacerbations account for more than 10% of acute medical admissions, and that many deaths occur during admission or shortly following discharge. For the patient this is associated with impaired quality of life, and an increased likelihood of readmission (Hosker *et al* 2006). Garcia–Aymerich *et al* (2003) comment that patients with COPD suffer recurrent exacerbations with worsening symptoms and a further reduction in lung function, which is associated with high healthcare cost as a result of hospital admission.

Risk factors for re-admission are clinical status, adherence to medication, lifestyle, quality of life and social support (Garcia-Aymerich *et al* 2003). Murphy *et al* (2005) also note that exacerbations of COPD are associated with a delay in lung function recovery of up to 12 weeks, during this period patients are susceptible to further exacerbation. Patients suffer a mean exacerbation rate of 2-4 per year (Seemungal *et al* 2000).

It is therefore feasible to suggest that expenditure could be minimised if admissions to hospital were reduced. Yohannes and Connolly (2004) state that a patient with moderate to severe COPD is on average likely to suffer three exacerbations per year, with an average hospital stay of eleven days

per exacerbation. Pitta *et al* (2006) also note the negative impact exacerbation has on healthcare resources and survival, suggesting that this was linked in part to periods of inactivity. Following a retrospective audit, NICE (2003) reported that of 1400 patients admitted with exacerbation that 34% were readmitted and 14% had died within 3 months.

Hospital Admission and Muscle Force

Repeated admission to hospital can have a profound detrimental effect on all aspects of the condition, and lead to a further decline in physical capacity and exercise tolerance. Peripheral muscle weakness is a known feature of COPD. An important piece of research which informs the current study was conducted by Spruit *et al* (2003) who demonstrated a decline in muscle strength in hospitalised patients suffering an exacerbation, compared with stable patients; it was suggested that peripheral muscle force declined throughout a hospital admission and was at its lowest at day 3. Possible causes were related to changes in nutritional, metabolic, oxidative and inflammatory responses at the time of exacerbation, in addition to bed rest. Peripheral muscle force declines in approximately 30% of all COPD patients (ATS/ERS 2006).

The results of Spruit *et al* (2003) showed that on admission hospitalised patients had lower mean Quadriceps muscle Peak Torque (QPT) (66 (22)% predicted) compared to stable patients, and that QPT declined between days 3-8 of admission, and that this may relate to the levels of circulating inflammatory markers Insulin-like growth factor I (IGF-I) and Interleukin 8

(CXCL8). Patients who have frequent exacerbations also have a faster decline in functional status than those with infrequent exacerbations, measured by quality of life questionnaires (Wedizcha and Wilkinson 2006).

Pitta *et al* (2006) conducted another important study which concluded that patients who suffered ≥1 exacerbation per year for which they were hospitalised showed decreased walking distances 1 month following, and patients with the lowest distances were the most likely to be re-admitted to hospital. This paper and the paper by Spruit *et al* (2003) indicate a need for some therapy to be aimed at the peripheral muscle.

Pulmonary Rehabilitation

The American Thoracic Society/European Respiratory Society (ATS/ERS) (2006) define rehabilitation as a comprehensive intervention, which has demonstrated reductions in dyspnoea, increased exercise tolerance and an improved health related quality of life. NICE (2003) suggest that pulmonary rehabilitation is a process used for patients with COPD, and is designed to optimise the individual's social and physical performance, and autonomy. The evidence in favour of rehabilitation is overwhelming in improving physical function and quality of life.

Although the consensus is that pulmonary rehabilitation is of benefit, it is not always available to those who need it. Clini *et al* (2001) report that although it is widely recognised that rehabilitation is effective in enhancing standard therapy and alleviating symptoms, that programmes are costly and facilities

are limited therefore careful selection of patients is required. Yohannes and Connolly (2004) comment that in the UK only a third of acute hospitals provide pulmonary rehabilitation.

Exercise training is at the cornerstone of pulmonary rehabilitation (Spruit 2004). Reardon *et al* (2005) concur by suggesting that since peripheral muscle dysfunction is a major cause of reduced function in COPD patients that physical training is vital to increase exercise capacity, functional status and quality of life.

Rehabilitation is important in the management of COPD, and exercise is a vital component of this. However for those suffering an exacerbation of their condition completing a traditional course of rehabilitation may be difficult as they are constrained by their symptoms. The aim of this study is to propose a novel way of maintaining physical capacity during an exacerbation, commencing while the patient is hospitalised; which as previously discussed is when physical capacity could be further diminished.

Puhan *et al* (2005) found that following successful rehabilitation immediately after exacerbation the mean numbers of readmissions to hospital were reduced from 1.6-0.9 in the following year. Previous research suggests that following exacerbation the recovery period is long. Puhan *et al* (2005) note that if rehabilitation is commenced during this period that it can improve prognosis and quality of life. Patients undergoing early rehabilitation were readmitted 30% less often than those in the control group, and there was a

trend towards fewer in-patient days (Man *et al* 2004).

Literature Review

This study is a rehabilitation based intervention commenced during the acute phase of the disease. Therefore this section will examine how to identify the impact of COPD on the individual, types of training that are commonly employed, the value of exercise training during an exacerbation of the disease; and the previous literature surrounding the rehabilitative strategies discussed.

ATS/ERS (2006) suggest that pulmonary rehabilitation programmes traditionally include patient assessment, exercise training, education, nutritional intervention and psychosocial support. Prior to rehabilitation it is imperative to undertake a thorough assessment of the patient's condition to tailor the rehabilitation to meet the needs of the individual. Reardon *et al* (2005) state that coordinated action is required by a multidisciplinary team in order to deliver individualised rehabilitation.

Assessment of Patients with COPD

Walking Performance

Cress *et al* (1996) state that physical performance tests have become popular due to concerns that self-reported function may provide insufficient information about disability. Schonhofer *et al* (1997) illustrate the validity of walking tests by stating that tests based on walking speed are widely used and consistently correlate with self-reported exercise limitation. Exercise testing in COPD varies from simple field tests to maximal laboratory tests that

necessitate the use of technical equipment (Arnardottir *et al* 2006).

To avoid the use of technical equipment field tests such as the 6-minute walking distance (6MWD) and the Incremental Shuttle Walk Test (ISWT) are employed. Behnke *et al* (2005) state that the 6MWD and the 6-minute treadmill walking distance have been introduced as measures of exercise capacity, and have shown a correlation between these measures and the activities of daily living. The ATS (2002) note that in the 1960's Balke formulated a simple test to assess functional capacity by measuring the distance walking during a specified time, and that this was a simple and practical test. The 6MWD demonstrates the most variability in its application, and that although these tests are useful objective measures for programmes it is unclear how they translate into activities of daily living (ATS/ERS 2006). The 6MWD may be more suitable for those with severe COPD due to its self-paced protocol (Turner *et al* 2004).

An alternative is the ISWT developed by Singh *et al* (1992) they described a walking test over a 10-metre course incorporating audio signals to control pace. Singh *et al* (1994) note that a benefit of this test is that it is externally paced and therefore influenced less by encouragement. Because it is incremental it stresses the patient to a symptom-limited performance. This is of benefit when assessing the outcomes of rehabilitation as it can be used to compare pre and post training responses at an equivalent level of intensity of exercise (Turner *et al* 2004). This was followed by the development of the Endurance Shuttle Walk Test (ESWT) formulated by Revill *et al* (1999) this

was designed to complement the ISWT in order to standardise walking speed and allow endurance exercise capacity to be assessed.

To summarise, the protocols are very different, the 6MWD is self paced and can be continuous or intermittent. The ISWT is externally paced and is conducted over a 10 metre course, and requires an increase in walking speed until the test is halted due to breathlessness or fatigue; or if the patient fails to reach the cone in the time allowed (Turner *et al* 2004).

Brcukink *et al* (1998) found that patients with chronic conditions such as COPD reported an increase in the perception of fatigue when in a clinical setting and that there is a relationship between subjective fatigue, pulmonary function and peripheral muscle force. A reason for this fatigue at peripheral muscle level is cited by Richardson *et al* (2004) who suggest that COPD patients display an increase in the proportion of type II muscle fibres, either assessed histochemically or by the expression of myosin heavy chains, the opposite in fibre changes is demonstrated in healthy ageing; the authors hypothesise that this change in fibre composition could be related to exposure to periods of reduced oxygen availability, or muscle disuse both of which occur in COPD.

It has been proposed that peripheral muscle weakness contributes to exercise intolerance. Bernard *et al* (1998) state that peripheral muscle weakness is commonly observed in patients with COPD and recently possible links to exercise intolerance have been recognised. Jones *et al* (2004) cited by

Reardon *et al* (2005) further suggest that muscle deconditioning occurs quickly as a consequence of muscle inactivity, this is because muscle mass and the expression of genes associated with muscle growth are reduced with muscle immobilisation.

Exercise tolerance can also decline due to a decrease in cardiovascular function secondary to inactivity. ATS/ERS (2006) illustrate this by stating that inactivity can lead to cardiovascular deconditioning, this deconditioning could also be exaggerated during a hospital admission. These factors could possibly be managed with the incorporation of pulmonary rehabilitation.

Breathlessness

Exertional dyspnoea is perhaps the commonest complaint of patients with COPD. Dyspnoea can be assessed in various circumstances, for example breathlessness during exercise exertion and breathlessness during the activities of daily living (Oga *et al* 2005). Patients with COPD often find it difficult to complete their activities of daily living. It is feasible to suggest that patients may be even more exhausted when undertaking exercise as part of a rehabilitation programme, particularly during an exacerbation.

The measurement of dyspnoea is important; its severity and impact on a person's functioning can be evaluated (Eakin *et al* 1998). Measurements of breathlessness can be taken using several different methods. Ozalevli *et al* (2006) state that one such method is the Modified Borg Scale (MBS) this is a modified form of the original Borg scale (Borg 1982) which rates perceived

exertion to measure symptoms such as breathlessness on a non-linear 10-point scale (appendix 1). They did however find that although this is a widely used scale that in their study there was, as anticipated no relationship between MBS and pulmonary function, and that the Medical Research Council (MRC) (appendix 2) scale appeared to be more compatible for noting change in FEV_1 values as they are both measured at rest. Therefore for this study both will be utilised. The MRC can also be used to assess how breathless a patient is at rest. Bestell *et al* (1999) confirm that the MRC dyspnoea scale has been used for many years to grade the effect of breathlessness on daily activities. Patients who demonstrate breathlessness during daily activities score an MRC 3 or above up to 5. The MRC is also of relevance as it correlates with the ISWT (Bestall *et al* (1999).

Quadriceps Strength

Garcia-Aymerich *et al* (2006) recommend that COPD patients should aim to maintain or increase levels of regular physical activity in order to reduce the risk of admission to hospital. A seminal paper by Pitta *et al* (2006) iterates that during hospitalisation patients had a very low level of physical activity and spent very little time in weight bearing activities. They reported that by day 8 of an admission quadriceps strength was significantly reduced. Spruit (2004) suggests that a reduction in a patient's functional capacity is closely related to quadriceps muscle weakness. Swallow *et al* (2007) also found that quadriceps muscle strength can add prognostic information to identify high-risk patients who may benefit from rehabilitation. Coronell *et al* (2004) illustrate the relevance of assessing quadriceps strength by stating that even

those with clinically stable COPD display impairment of the quadriceps.

Studies have indicated that quadriceps strength and cross-sectional area are associated with the degree of airflow limitation, a positive relationship was found between predicted FEV_1 percentages and quadriceps strength ($r=0.55$, $p<0.0001$) suggesting that there is a correlation between a decrease in FEV_1 translating to a decrease in quadriceps strength (Bernard *et al* 1998). Bernard *et al* (1998) also note that malnutrition and hypoxia can contribute to muscle weakness, and although a patient may present with a normal BMI this does not exclude malnutrition as a factor in muscle weakness because muscle mass is lost faster than body weight. Therefore although body mass is a prognostic factor in COPD, studies show that mid-thigh cross sectional area is more closely related to survival than body weight (Marquis *et al* 2002). O'Shea *et al* (2004) suggest that quadriceps muscle cross-sectional area can be increased by up to 8% following strength training.

These findings suggest that the quadriceps would be a valid muscle to focus on when implementing involuntary muscle training in rehabilitation during an acute exacerbation. The quadriceps femoris is an important muscle to concentrate on in rehabilitation programmes as identified above. One further reason for this is illustrated by Salman *et al* (2003) who conducted a meta-analysis surrounding respiratory muscle training. They concluded that research into exercising respiratory muscles alone demonstrated no significant improvements in exercise tolerance between the experimental and control groups. Whereas trials that incorporated lower extremity training

showed that the experimental rehabilitation groups did significantly better in dyspnoea and walking tests. There is also a relationship between muscle weakness and the use of steroids (Decramer *et al* 1997). This provides another contributing factor for a decline in quadriceps strength.

It could be hypothesised that during an admission for exacerbation that physical activity will be reduced contributing to further quadriceps muscle weakness. Spruit *et al* (2003) found that muscle force was significantly reduced during a hospital admission, they noted that between days 3-8 quadriceps peak torque decreased 5% of predicted (95% CI –22 to 8, p=0.05). Pitta *et al* (2006) concur by suggesting that following an 8-day admission to hospital for exacerbation that there was a significant reduction in quadriceps strength (median –5% of the predicted value) ([IQR –1 to –12%] p=0.04).

However the authors note that the decline in quadriceps strength may be caused by underlying factors which attribute to inactivity; the authors also noted just how strikingly inactive patients are during hospitalisation by day 2 patients only spent a median of 7% of time in weight bearing activities by discharge this had only increased to 9%. They noted that during admission muscle force decreased by 7% predicted, when you consider that following 6 months of rehabilitation muscle force only increases by 20%, a loss of 7% in 5 days seems very relevant. Tudor-Locke *et al* (2008) note that previous studies recommend 10000-12000 steps should be taken per day to improve exercise tolerance.

This implies that in hospital there is pronounced inactivity that is a significant contributing factor in the decline of muscle force. The findings of these seminal papers illustrate the importance of intervening early on in an exacerbation and while patients are hospitalised in a bid to halt further decline in muscle force and physical function.

There are several different methods which can be adopted to ascertain quadriceps strength. The most common method used is Isometric Maximum Voluntary Contraction using isokinetic dynamometry, there are also handheld dynamometers which do not require taking the patient out of the ward area to use the equipment. A study by Martin *et al* (2006) noted that the handheld method was valid for quick and objective measurement of quadriceps strength in the clinical setting. However the handheld method relies on the user having enough strength to resist the muscle force that the subject is able to generate. Other more sophisticated methods of measuring the quadriceps cross sectional area include Computerised Tomography (CT) and Magnetic Resonance Imaging (MRI) scanning; ultrasound is an alternative less costly method which can be used at the bedside. Femoral nerve stimulation can also be incorporated, although it is the gold standard it is not widely available and is expensive (Seymour *et al* 2009). Chair fixed dynamometers can also be used. Gagnon *et al* (2005) conducted a study which aimed to validate the chair fixed dynamometer as a strain gauge measure; they concluded that high indices of inter-trial and inter-rater reliability were found validating its use in the clinical setting; however the chair fixed dynamometer and isokinetric

dynamometry should not be used interchangeably.

Activities of Daily Living and Quality of Life

A broad assessment of daily activity can be gained from the use of questionnaires. Puhan *et al* (2005) state that clinicians recognise the importance of measuring health-related quality of life as an important outcome measure in clinical trials for those suffering with COPD and other respiratory illnesses. Although current guidelines define the severity of COPD in terms of FEV_1 measurements, other health status measurements may well complement FEV_1 results when characterising the impact of a person's disease (Bestall *et al* 1999).

Health Status

As previously outlined NICE (2007) state that the MRC dyspnoea scale can be used to grade the patient's perceived breathlessness on daily activities in the patients usual state. Bestall *et al* (1999) suggest that this is a simple valid method of categorising COPD patients with their disability. The Chronic Respiratory Questionnaire (CRQ) (appendix 3) is another commonly used assessment tool. This tool has 20 questions about the level of disability in the domains of dyspnoea, fatigue, emotional function and mastery (Guyatt *et al* 1987). Patients score their level of impairment on a scale of 1-7 in each portion of the questionnaire. The authors found that because the CRQ is disease specific it is more responsive when compared to generic tools when evaluating pulmonary rehabilitation. Williams *et al* (2001) found that when the CRQ was self-reported as opposed to interviewer led it gave patients a

greater sense of privacy, and that results were comparable to the gold standard interviewer led version.

Anxiety and Depression

The Hospital Anxiety and Depression scale (HADS) (appendix 4) assesses emotional state (Zigmund and Snaith 1983). This questionnaire comprises of 14 items, which separately assess anxiety and depression. They score up to 21 and a score of over 10 indicates significant levels of anxiety or depression. Studies have found that depression in COPD can be related to functional status, and that this may correlate with medical consumption (Decramer *et al* 1997).

Activity Monitoring

Previously activities of daily living were estimated by the use of questionnaires or diary keeping, however self-reporting can often be inaccurate. Pitta *et al* (2005) advocated the use of activity monitors over questionnaires, suggesting that 69% of respondents overestimated their walking time. If self-reporting was a sole measurement in a piece of research this could lead to highly erroneous results of time spent walking and distance travelled. Daily activity can be measured using an activity monitor. Schonhofer *et al* (1997) reported that repeatable measures of daily activity could be gained from simple pedometers, however more useful were monitors which not only recorded numbers of steps taken but also vertical motion not just motion of the legs.

There are some concerns over the responsiveness of the motion sensors, for

example there are some activities in daily life and in exercise programmes that do not include total body movement, possibly isolated upper body movement (Pitta *et al* 2005). Therefore any monitor used needs to be sensitive enough to detect these activities, a multiaxial device may offer a solution. Once calibrated to walking speed, activity monitors can differentiate between normal walking speeds and those prescribed as part of rehabilitation (Hunter *et al* 2006).

Singh and Morgan (2001) further advocate the use of activity monitors by suggesting that they have the ability to differentiate between brisk walking and low-level domestic activities. The importance of a moderate level of daily activity was iterated by Garcia-Aymerich *et al* (2003) who note that patients with COPD who have a high level of daily activity are at a reduced risk of readmission due to exacerbation, the third of patients who reported undertaking ≥60minutes a day of an activity equivalent to walking, displayed a reduction in the risk of readmission to hospital of up to 50%. Garcia-Aymerich *et al* (2006) reiterated their findings by stating that a follow up study of 2386 patients over a 20 year period found that a level of physical activity equivalent to walking or cycling for up to 2 hours a week was associated with a reduction in hospital admission of 30-40%. Their results noted that subjects reporting a low, medium or high level of physical activity had a lower risk of re-admission to hospital compared to those who reported a very low level of physical activity. Incidence rate ratio 0.72, 95% confidence interval (CI) 0.53-0.97.

Treatment

Exercise training

Exercise is a vital component of pulmonary rehabilitation. The ATS/ERS (2006) indicate exercise training for those with decreased exercise tolerance, exertional dyspnoea, fatigue and impairment of activities of daily living in stable COPD. There is however controversy over the optimal training regime to adopt. Bernard *et al* (1999) state that although exercise training is an essential component of rehabilitation there is no consensus over the optimal strategy.

Strength Training

Spruit *et al* (2002) define strength (resistance) training as a mode of exercise in which small groups of muscles are trained by the lifting of weights. Training sessions generally comprise of 2-4 sets of 6-12 repetitions at intensities ranging from 50-85% of one repetition maximum (ATS/ERS 2006). Spruit and Wouters (2007) reported that resistance training improves skeletal muscle force, and identified that a major advantage of this training is that is places less strain on the respiratory system. Resistance training can also be used for selective muscle training by the repetitive lifting of weights; this can be individually adapted to the needs of the patient (Spruit *et al* 2002).

O'Shea *et al* (2004) state that strength training alone; based on 6-12 repetitions of each exercise at an intensity ranging from 50-85% of one repetition maximum, is unlikely to cause change in aerobic capacity, and that more research would be needed to detect changes, if any in the cardiovascular fitness of patients. Mador *et al* (2004) reiterate this by reporting

that while strength training made muscles stronger this did not translate into improvements in exercise capacity.

Endurance Training

ATS/ERS (2006) state that walking and cycling are the most commonly applied modalities in endurance training. Endurance training commonly uses cycle ergometry, treadmill walking and arm cranking to achieve a peak workload, often based on perceived levels of dyspnoea or fatigue (Spruit *et al* 2002). Sala *et al* (1999) state that endurance training including lower limb exercises have been consistently shown to relieve dyspnoea, and improve health related quality of life. Maltais *et al* (1996) hypothesised that a controlled endurance training programme could partially correct early rises in blood lactate levels and low concentrations of skeletal muscle oxidative enzymes in patients. Sala *et al* (1999) concur by reporting that improvements after endurance training were related to enhanced skeletal muscle bioenergetics rather than changes in ventilation. Their results showed that oxygen consumption (VO_2) increased by 10-15% in the COPD patients and the control group (13-20%).

Morgan (2005) states that most training centres on endurance training, which will improve exercise performance but will not affect the strength or mass of muscles. Spruit *et al* (2002) advocate resistance training as an alternative for patients who have difficulty in completing a high intensity endurance programme; although high intensity endurance training has been associated with significant improvements in peripheral muscle strength, dyspnoea and

quality of life.

Combined Training

It is most likely that a combination of approaches would be optimal, incorporating strength and endurance training. Ortega *et al* (2002) reiterate this by suggesting that in their study the combined training group acquired most of the benefits of intervention, and that would provide an optimum strategy. They found that after 12 weeks of training that the duration of exercise was significantly higher in the combined group, than in the group who undertook strength training only (48.9±29 minutes) ($p<0.01$) versus (43.6±21 minutes).

Bernard *et al* (1999) also found that combining strength with aerobic training is associated with significant increases in muscle strength (20±12% versus 8±10% [mean±SD]) in the aerobic only group; and muscle mass increases of the quadriceps and pectoris major 8±13% and 15±9% respectively ($p<0.001$). There was an increase in latissimus dorsi muscle after training of a similar magnitude in both groups. These findings did not provide significant improvements in exercise capacity or quality of life.

Interval Training

Interval training constitutes periods of high intensity exercise followed by short periods of rest. Spruit and Wouters (2007) state that 20-40% of patients do not complete conventional rehabilitation programmes therefore it is reasonable to speculate that regular programmes do not meet the needs of all

patients. Vogiatzis *et al* (2002) advocate the use of interval training by reporting that it allows maximum exercise to be taken with a relatively low perception of dyspnoea, as breaks are taken regularly. Kamahara *et al* (2004) elucidate by noting that since it is difficult for patients to carry out exercise for long periods due to shortness of breath, interval training has been found to be more beneficial. For patients suffering an exacerbation of their disease, initially any form of physical exercise may prove too strenuous and cause patients to become dyspnoeaic.

Involuntary Training

General exercise training is of course voluntary; however during an exacerbation patients may feel too constrained by their symptoms to participate in such training, therefore rehabilitation incorporating involuntary training may be of benefit at this time. One such method is Neuromuscular Electrical Stimulation (NMES). Bax *et al* (2005) state that applying an electrical current to neuromuscular tissue triggers muscular contraction and that its objective is to improve fundamental muscle properties, intramuscular blood flow, maximum force output, and force endurance through repeated repetitions. Bourjeily-Habr *et al* (2002) iterate that stimulation can increase muscle capillary/fibre ratio, fibre cross-sectional area and the number of fibres. Holcomb (2005) concurs that electrically induced muscle contractions involve a selective recruitment of type II muscle fibres; because type II fibres are innervated by large nerves they display a lower resistance to electrical currents.

Ward and Shkuratova (2002) state that NMES preferentially recruits fast twitch fast fatigue motor neurons. Muscle force is generated by two means, firstly central nervous system adaptation and fibre recruitment; and secondly by building muscle bulk. NMES can take place directly over the target muscle or indirectly by placing pads over the nerve trunk.

This involuntary training could be particularly useful for COPD patients because it would optimise muscle properties without causing stress through worsening dyspnoea. NMES can improve lower limb ambulation, strength and endurance for those with incapacitating dyspnoea (Neder *et al* 2002). Holcomb (2005) concluded that NMES is not an adequate substitute for traditional resistance training, however these conclusions were reached by studying athletes not COPD patients for whom completion of traditional resistance training may not be feasible. Spruit and Wouters (2007) suggest that for those patients with prolonged respiratory failure, that NMES can be used to improve skeletal muscle strength and maintain muscle mass during periods of immobilisation. Ip *et al* (2004) concur by stating that the exercise component of rehabilitation for frail patients should be low-impact and it is beneficial if the in-patient stay is short so that patients can return home. It is feasible that NMES could potentially minimise the period of admission, if commenced early.

NMES

NMES unit

NMES has already been widely used to rehabilitate chronic conditions such as Chronic Heart Failure (CHF). Nurh *et al* (2003) investigated whether low frequency electrical stimulation (15Hz) of the quadriceps femoris could counteract detrimental changes in skeletal muscle. Their findings suggested that stimulation was beneficial as a treatment for improving physical condition and exercise tolerance. Dobsak *et al* (2006) demonstrated that stimulation could effectively counterbalance decreased physical capacity by increasing oxidative enzyme activity in skeletal muscle fibres. Harris *et al* (2003) note that in Chronic Heart Failure rehabilitation intervention may have benefits in reducing admission rates and mortality. Nurh *et al* (2003) suggest that data concerning the effects of muscle stimulation on patients with chronic conditions was scarce. At present there are only a few published studies incorporating NMES into COPD rehabilitation.

Bourjeily-Habr *et al* (2002) hypothesised that electrical stimulation of the lower extremities could improve muscle strength and exercise tolerance in patients with moderate to severe COPD. Their study took a sample of eighteen patients who were recruited if they had a FEV_1 of <65% of predicted value,

were below 70 years, and had self reported exercise limitation; and were otherwise medically stable. Patients were excluded from the trial if they had cardiovascular and neuromuscular disease, joint disease, previous pulmonary rehabilitation; or had recently suffered an exacerbation.

Patients were randomised into a control and experimental group. Electrical stimulation was performed for 20 minutes a day on each limb for a 6-week period. The protocol adopted provided impulses of 50Hz lasting 200ms every 1500ms, in an asymmetrical square wave pulse. Intensities were set to create a visible contraction ranging from 55mA to 120mA. The intensities were increased by 5mA each week. The control group used the same setup but received no active stimulation.

The findings of Bourjeily-Habr *et al* (2002) suggested that stimulation improved muscle strength and exercise capacity, quadriceps strength was improved significantly for the treatment group from 44.7 (6.5) to 55.2 (6.6) Nm units p=0.004; an increase in the ISWT illustrated a mean improvement of 36.1% for the treatment group compared with 1.6% in the sham group (p=0.007). The conclusions of the study show that NMES may be used as a rehabilitative strategy however further research may be needed, as 18 is a small sample size. Further studies are needed to examine the long-term effects of stimulation and the mechanisms by which it works (Bourjeily-Habr *et al* 2002). However Bourjeily-Habr *et al* (2002) do note that stimulation does improve muscle strength and exercise capacity in COPD and could be a useful component in rehabilitation.

Neder *et al* (2002) also explored NMES in stable COPD, again only using a small sample of 15 patients and used a training protocol, which centred around a symmetric biphasic square pulsed current at 50Hz (unlike the Bourjeily-Habr *et al* (2002) paper which used an asymmetrical waveform). In the first week the cycle was 15 minutes on each leg with 2 seconds on and 18 seconds off. The second week it was applied to the leg for 30 minutes 5 seconds on and 25 seconds off, then 10 seconds on and 30 seconds off thereafter. Patients were asked to continue up to the highest tolerable amplitude. This was conducted on an out-patient basis.

The findings of Neder *et al* (2002) concurred with those of Bourjeily-Habr *et al* (2002) that after a 6-week period, stimulation improved some markers of skeletal muscle strength and endurance of COPD patients, there were significant differences in maximal isokinetic strength (using an isokinetic dynamometer), difference between mean isometric force 21.2 (-10.8 to 53.2) Newtons (N); and muscle fatigue index % (difference between means –23.2 (-42.5 to –3.9) were found between the two groups in favour of NMES, however indices of muscle endurance such as mean power and total work did identify trends towards improvements however not to a significant level. NMES did result in significant improvements in whole body incremental and exercise peak oxygen uptake (VO_2) during endurance following NMES mean VO_2 increased by 0.13% (95%CI 0.03-0.23) $p<0.05$, this was significantly higher than the group undertaking a control period, and despite the differences in training protocol. Again, the authors also recognised that they were limited by

the small sample size.

More recently research carried out by Vivodtzev *et al* (2006) recruited a sample of 17 in-patients who had recently suffered exacerbation, or had been admitted to an intensive care unit (FEV_1 30±3%). Their study took place over one month all patients were randomly assigned to usual rehabilitation or rehabilitation plus NMES. Vivodtzev *et al* (2006) concluded that NMES did improve quadriceps strength and dyspnoea when performing daily activities; however this increase in quadriceps strength did not correlate with better results in the 6 minute walking distance. They noted that changes in muscle strength were correlated to changes in muscle mass (r=0.94; p=0.03 [spearman correlation]). Although there was an increase in 6MWD (63±40m; p=0.01) in the treatment group, the between group difference was not significant (p=0.12). This is possibly due to the fact that the patients recruited for the study were more severely deconditioned and malnourished, whereas in the previous studies subjects were stable, therefore their improvements were bigger.

Following treatment Maximal Volitional Contraction (MVC) of the quadriceps using an isokinetic dynamometer significantly increased in both groups. The group which did NMES plus traditional rehabilitation demonstrated an increase in MVC (97±71 contractions; increase 35%). Vivodtzev *et al* (2006) reported that MVC was increased by (36±35 contractions increase 14% p=0.03) in the group which completed traditional rehabilitation only. Therefore although increases were significant for both groups there was a two-fold

improvement in the NMES group.

A study conducted by Zanotti *et al* (2003) recruited 24 in-patients from an intensive care unit suffering from respiratory failure due to COPD and applied square wave symmetric impulses from 8-35Hz for up to 30 minutes per day for 28 days. They found that subjects had improved peripheral muscle strength (2.16±1.02 vs 1.25±0.75, p=0.02) (muscle strength scored from 0-5), which resulted in being able to sit out of bed earlier, and consequently that their duration in intensive care was shortened. The NMES group were transferred from bed to chair 10.75 ± 2.41 days versus 14.33 ± 2.53 days for the control group. Again this study advocates the use of NMES, and although the sample were all mechanically ventilated they were medically stable and excluded if suffering from an exacerbation of their COPD. Therefore they were most likely to be long term patients weaning from the ventilators due to poor lung compliance. It is difficult to make direct comparisons between the improvements in muscle function in this study and the previous noted because an arbitrary scoring system was used opposed to objective measurement. The patients chosen for this study represented the closest available to a true control group as all of the patients had been confined to bed.

A recent crossover study conducted by Dal Corso *et al* (2007) found that following 6 weeks of NMES at a frequency of 50Hz NMES caused a significant increase in type II muscle fibres, and a decrease in type I cross sectional area (median change range)=12.5% (-16.8% to 57.6%) vs -9.8% (-

40.8 to 36.6%) ($p<0.05$). This did not correlate with significant improvements in isokinetic quadriceps strength or the 6MWD. Following NMES peak torque was 103.2±50.6Nm and 6MWD 502±68m, for the sham group peak torque was 101.8±37.7Nm and for the 6MWD 500±56m there was no significant increase $p>0.05$ for either group. 6MWD results were high this could be related to the patients studied who were all stable outpatients demonstrating an MRC II-III score. Dal Corso *et al* (2007) reiterate that a reason for the discrepancies in results between their study and previous ones is that this study evaluated patients who were not severely impaired. It is likely that NMES is more effective for those possibly recovering from an exacerbation of COPD; however this hypothesis would need adequately testing (Dal Corso *et al* 2007).

These studies are all limited by their small sample sizes, and the authors suggest that larger trials are required to validate the findings of preliminary trials and elucidate on the most effective protocol. A review by Sillen *et al* (2009) implies that improvements following NMES appear to be clinically relevant, the mean increase in ISWT distance between sham and therapeutic stimulation in the studies they reviewed was 68.8metres; above the 47metres required to mark a clinically significant improvement.

It would appear that all of the studies reported excluded patients suffering exacerbation. Zanotti *et al* (2003) state that NMES is safe and reliable and can be performed in any hospital setting; therefore it is feasible to suggest that it could be performed on patients admitted with an exacerbation of their

disease. Intervention at this time could improve muscle strength without causing dyspnoea as illustrated by previous research. Neder *et al* (2002) elucidate this by stating that during the trial period four patients suffered a mild exacerbation but were able to continue with the protocol without any adverse events. A review by Roig and Reid (2009) noted that at present NMES has the potential to be used as an adjuvant therapy to rehabilitation, that it may only be beneficial as a primary intervention during the acute phase of illness when a patient is confined to bed.

There is not however any consensus about the best protocol of NMES to be used. An example of this is that the study by Vivodtzev *et al* (2006) which incorporated a longer duty cycle (contraction/relaxation time) than that of the other studies, does this have any discernible effect on the outcome measures of the study?

Application/ protocol

Ward and Shkuratova (2002) reported that early work carried out in Russia advocated use of the 10:50:10 protocol for NMES, where stimulation would be applied for 10 seconds followed by 50 seconds rest for 10 minutes. However although this is still widely used there is little published evidence to support this protocol. After evaluating previous work, Ward and Shkuratova (2002) conclude that there needs to more comparison studies into whether this ‘on’ ‘off’ regime is the most effective. Despite this it is variations on this regime which are most widely used in the reported studies.

Laufer *et al* (2001) conducted a study comparing three different waveforms; monophasic, biphasic, and polyphasic waveforms. The first two generated by a battery-powered stimulator that could be used in a patient's home, and the polyphasic waveforms generated by alternating current driven stimulators used in clinics. They reported previous research shows that for recovery of quadriceps strength, higher intensity clinical stimulators were recommended. This is important because research into portable stimulators could decrease expenditure, and could be used at home. The authors found that results from battery-powered stimulators illustrated that waveforms were comparable to those generated by those used in clinics. It is also worth noting that Laufer *et al* (2001) were investigating quadriceps strength of volunteers with a mean age of 28.2 years with no muscular or skeletal impairment. It is possible that for COPD patients with peripheral muscle weakness that lower intensities may be effective as previously illustrated.

Differences between portable and clinical stimulators have also been reported by Lyons *et al* (2005). Their study used the Empi-300PV™, which is used for this study. This is a multifunction electrotherapy device capable of providing NMES to activate specific muscles. Lyons *et al* (2005) reiterated the findings of Laufer *et al* (2001) by stating that both stimulators produced comparable levels of quadriceps muscle torque (using a computerised dynamometer) when the subject's maximum tolerance was used as the criteria for the selection of stimulus, this means that the subjects only increased intensity to a level that was comfortable for them.

Therefore it is possible to stimulate a training load for NMES that can be used by patients in their own home. It is also worth noting that in relation to the Empi-300PV™ that for the stimulation of large muscles that a symmetrical waveform should be used as stated in the accompanying handbook, however in the studies conducted by Bourjeily-Habr *et al* (2002) and the study by Zanotti *et al* (2003) asymmetrical waveforms were used. Hinghe and Sluka (2006) suggest that when a symmetrical waveform is used that there is no potential for a chemical reaction to occur under the electrodes, whereas with an asymmetric waveform there is potential for chemical reaction, which could result in discomfort for the patient. Although the study by Hinghe and Sluka (2006) found that there was no significant difference in perceived comfort.

Length of intervention is also important most of the studies took place over a 6-week period for 30 minutes a day. Bax *et al* (2005) illustrate the validity of this protocol by reporting that following a systematic literature review, that studies using NMES at high intensity for 3 weeks were not as effective as NMES conducted at lower intensities for a training period of up to 8 weeks (generally frequencies between 30-100Hz are recommended). Therefore a training period of 4-6 weeks should give reliable results; the waveform adopted was not specified. Many patients experiencing an exacerbation take a long time to recover, therefore rehabilitation and NMES need to be tailored to fit this timeframe.

Recovery from acute exacerbation

Quality of life recovery from an acute exacerbation appears in two phases, an

initial fast improvement in the first four weeks; and a second slower progression which can take up to several months the greatest improvements in the Saint Georges Respiratory Questionnaire were noted in the first 4 weeks 8.9 (14.6) units, however this was a greater improvement than that noted over the next 4 months due to a significant improvement between weeks 4-12, 4.1 units (95% CI 2.2 to 5.9, $p<0.0001$) (Spencer and Jones 2003).

All of the aforementioned studies utilised NMES for patients with stable disease. This study will recruit patients when admitted to hospital with an exacerbation of their disease. Murphy *et al* (2005) suggest the principle of rehabilitation medicine is that early intervention can improve mobility and prevent muscle atrophy; their study concluded that it is useful for COPD patients to commence rehabilitation as early as possible.

Value of Intervention During Exacerbation

Man *et al* (2004) advocate the introduction of early rehabilitation by suggesting that despite optimum medical treatment, when discharged patients take a long time to regain baseline levels of functioning It has been illustrated by previous studies that NMES can be effective in maintaining physical capacity as an adjuvant therapy for those with stable disease; therefore it is feasible to assume that it could be of benefit if incorporated into early rehabilitative strategy for those suffering an exacerbation. This could not only provide scope for further research but also implement changes in practice to benefit the long term care of COPD.

The hypothesis for this study is that NMES is effective in maintaining peripheral muscle strength during an exacerbation of COPD. The null hypothesis for this study is NMES will not be effective in contributing to the maintenance of physical capacity during an exacerbation of COPD.

Methodology

Subjects

Prior to commencing the study ethical approval was granted by the NHS Research Ethics Committee and NHS Research and Development (appendix 11). All patients considered for participation in the study were admitted to hospital with an exacerbation of their COPD. A sample of twenty patients were randomised into a treatment or control group using a sealed envelope method. Informed consent (appendix 8) was sought from all patients involved in the trial. Patients were not considered for the study if they had any contraindications to the NMES unit for example if they had a pacemaker fitted. Patients' consultants were informed of participation (appendix 9) and information sheets were supplied (appendix 10). Appropriate patients were supplied with information sheets on the first working day after admission, and were consented 24 hours after.

Study Design

A randomised controlled single blind trial was conducted to examine the effects of NMES on physical capacity in patients suffering from an exacerbation of their COPD. All patients were informed that they would be randomised into a treatment group using a therapeutic NMES regimen, or into the control group who would receive a 'sham' NMES technique at sub-therapeutic levels, patients would not know which group they were in, however they would know that there were two groups. The author of the study was not aware of which group patients were allocated into, although two other

pulmonary rehabilitation practitioners were not blinded to the patient allocation. All patients were evaluated at the beginning of the study, on discharge from hospital; and they were then recalled 4 weeks after commencing (4 weeks after the day of recruitment) the study for follow-up data to be taken.

Measurements

Baseline Data

Initial evaluation consisted of pulmonary function tests, an ISWT and measurement of quadriceps strength by strain gauge measurement. MRC scores were also taken, patients were asked to rate their MRC score in their usual state prior to admission to hospital. Patients were also given the HADS and CRQ questionnaires to complete in their own time. Patients were asked to wear an activity monitor during their stay in hospital, if the admission was prolonged the monitor was to be worn up to a week (appendix 5).

BMI

Patients consented into the trial were asked to submit their height (centimetres) and weight (kilograms) using Seca™ weight chair, in order to calculate their BMI, or values were taken from recent medical notes.

Pulmonary Function Tests

Pulmonary function tests were performed by Spirometry, FEV_1 and FVC measurements were taken. Participants were asked to perform three maximal forced expiratory breaths; these were taken while the patient was seated. The

spirometer used was the Micro Lab™ by Micro Medical Limited™.

Exercise Tolerance

In order to assess exercise tolerance, an ISWT was performed by those able, their dyspnoea and perceived exertion were assessed using the Modified Borg Score. As standard practice oxygen saturations were monitored throughout the ISWT using the Konica Minolta Pulsox 3™. Supplemental oxygen was provided for those who required it; if on long term oxygen therapy, or prescribed it while in hospital. Patients were asked to walk the 10 metre course and asked to adjust their pace as the audible cues dictated for as long as they could. A 10-metre course was set out using string between two cones. The compact disc of audible cues was commenced and the patient started to walk with an assistant between the cones and then waited at the other cone for the audible cue before returning to the other cone. The test was ended if the patient could no longer keep up with the audible cues or if they themselves stopped due to fatigue or dyspnoea. If able, patients completed an ISWT on commencing the trial, again on the day of discharge from hospital, and when recalled at 4 weeks. If tolerated patients completed a total of 3 ISWT's. Only standard encouragement was given, and the pulmonary rehabilitation practitioners completed the walks in a standard manner; they walked with the subject and gave them cues on when to walk and when to wait until the audio cue had sounded.

Quadriceps Strength

The Patients quadriceps strength was assessed using a strain gauge; a

dynamometer based on a Vernacare commode chair™ and Kern electrical balance unit™. The unit was calibrated by holding down the on/off button when the unit was switched on and checking that the readout was zero prior to the subject commencing the procedure. The procedure entailed patients sitting on the commode chair and pushing themselves back as far as possible to maintain good posture and ensure that the leg was hanging freely (90° hip and knee flexion). The patient was then strapped in and asked to keep their hands in their lap and not on the arms of the chair. A strap was secured around the leg and the patient was asked to extend their leg out as hard as possible and hold it during a count of three, then to relax; this was repeated five times, only on the patients strongest leg, corresponding to which hand they use.

The Kern™ unit possessed a hold button which was pressed when the subject had kicked out their leg and the readout had stabilised, therefore when a plateau had been reached the measurement was taken. The initial strain gauge measurements were in kilograms in order to convert this to Newton metres values were multiplied by 9.087. The mean average of the five measurements was taken for the purposes of this experiment. Patients were given standard encouragement only; prior to the last of the five measurements they were encouraged to make an extra effort.

Strain gauge chair

Activity Monitoring

During their stay in hospital patients were requested to wear an activity monitor (Bodymedia Sensewear Pro2™). The monitor was worn on the right arm around the bicep muscle. The monitor acts as a metabolic monitor displaying Total Energy Expenditure (TEE), Active Energy Expenditure (AEE), Metabolic Equivalents (METS), number of steps taken, Physical Activity Duration (PAD), sleep duration and time spent lying down, these are displayed using Sensewear™ professional software. The only times this was to be removed was when bathing, and when daily administration of NMES was taking place in order to minimise the electrical interference. For the purpose of this study only number of steps will be examined.

Activity monitor

Questionnaires

Patients were also asked to rate their dyspnoea on the MRC scale (MRC 2007) and the HADS (Zigmund and Snaith (1983) and self-reported CRQ (Guyatt *et al* 1987) were given out for patients to complete (see appendices).

On Discharge from Hospital

When a patient was ready for discharge they were again asked to repeat the ISWT and the quadriceps strength measurements were taken. Patients were supplied with their NMES unit, spare pads and batteries; and also a diary sheet for them to keep a record of intervention. They were supplied with the telephone number of the hospital in case of any problems and reassured that they would be phoned on at least a weekly basis to check progress; information sheets were also given (appendix 6). This intermediate data was not collected if patients were discharged unexpectedly following the collection of baseline data, or if the patient was an in-patient for the entire study.

4-Week Follow-up

At the end of the four-week period patients were recalled to complete follow-

up data. The ISWT and quadriceps strength measurements were repeated. In addition to the physical tests patients were given follow-up CRQ (Appendix 7) and HADS questionnaires to complete. Patients were asked if they would like feedback at the completion of the study and then discharged.

NMES Protocol

The machine used for the trial was the EMPI 300PV™. The unit comprises four surface patch electrodes two for each leg, one to be applied to the top of the quadriceps muscle and one for the bottom of the muscle. The size of the pads was 5×9cms. On commencing the trial patients were supervised until able to apply the pads correctly and use the controls, they were also provided with an information sheet for guidance.

Treatment Protocol

The treatment protocol was based on the regime adopted by Bourjeily-Habr *et al* (2002). This was comprised of a pulse rate of 35pps, symmetrical biphasic waveform, using a synchronous cycle with an on time of 10 seconds and an off time of 5 seconds. The timer was set at 30 minutes. This would be continued on a daily basis for a 4-week period. The rationale for this regimen was that it was the programme proposed for the treatment of disuse atrophy, and can be used for larger muscle groups. A frequency of 35Hz was used as opposed to 50Hz as used in the Bourjeily-Habr *et al* (2002) research because the previous studies which selected a sample as disabled as the sample in this current study used a frequency of 35Hz. Patients were given guidance on how to apply the device and requested to increase the amplitude to a

tolerable level or until they could see a visible contraction of the muscle. Patients in the treatment group were also advised to take a walk each day until constrained by their symptoms.

Control Protocol

The control regimen was based on a conventional Transcutaneous Electrical Nerve Stimulation (TENS) setting pulse rate 100Hz, synchronous channel cycling, and symmetric biphasic waveform. The timer was also set at 30 minutes and patients applied the unit daily for a 4-week period. The subjects were asked to increase the intensity to a tolerable level or until they could feel a tingling sensation. The reason TENS was chosen as the 'sham' technique was in case two subjects, one from each group began to discuss the trial it would be obvious to them which group they were in if one stated they had to increase the intensity and the other had been advised not to change the settings. The control group also took part in activities advised by the staff in the Active Therapy Unit such as using pedals or daily supervised walks. Both groups were advised to undertake physical as able, when visited by the research team subjects would be asked if they wished to be accompanied on a walk as far as possible until constrained however this was not compulsory only advised, all other aspects of care were comparable for both groups.

Exclusions

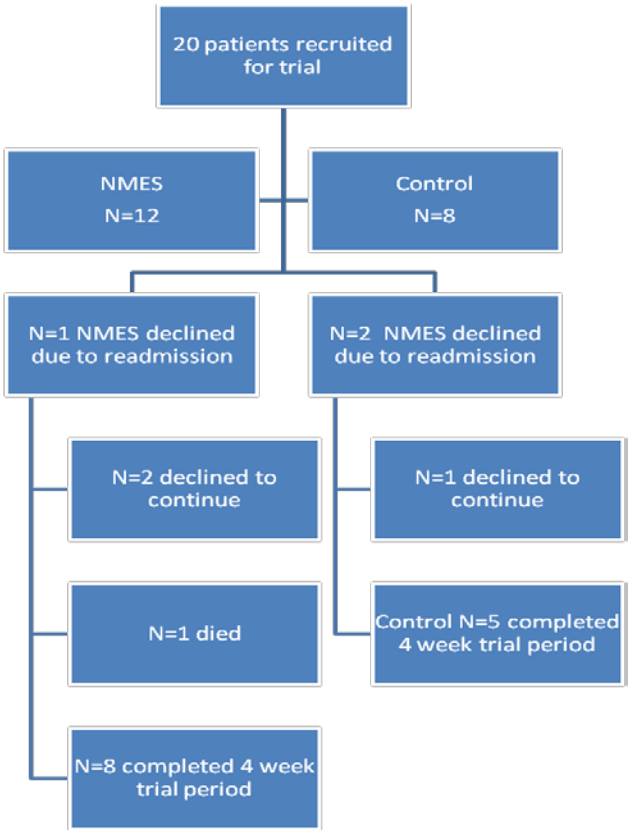
Patients were excluded from the trial if they were re-admitted to hospital during the trial period, and therefore would not have used the unit, or if they declined to continue the trial.

Statistical Analysis

The results will be analysed using the Statistics Package for Social Sciences (SPSS) issue 15.0. Baseline characteristics of the two groups will be expressed as the mean Standard Deviation (SD). Comparison between the two groups will be expressed as the mean difference with a 95% Confidence Interval (CI), in relation the FEV_1, ISWT and Strain Gauge (SG) (quadriceps strength) measurements. Between the groups baseline data will be subjected to an independent T-test. To compare pre- and post treatment data within the group a paired T-test will be used. Non-parametric tests will be used to analyse the data generated from the perception scales and questionnaires. The non-parametric tests used will be the Wilcoxon signed ranks test, followed by the Friedman test to compare group data. Strain gauge and shuttle walk data collected at the three time intervals will be analysed using repeated measures ANOVA. The primary outcome measures will aim to ascertain whether physical capacity measured by SG and ISWT data is maintained throughout the 4 week trial period. The level of statistical significance was set at $p<0.05$, however outcomes which reach a level of statistical significance will be viewed with caution due to the possibility of type I errors. Due to recruitment difficulties individual plots of data are also reported for measures of strength and performance in the ISWT. No formal power calculations have been employed. This can be viewed as a pilot study collecting data to inform a wider study looking at physical interventions during an exacerbation. The aim is to explain feasibility and effectiveness in maintaining physical capacity during an exacerbation of COPD.

Results

Flow chart for patients included in trial from recruitment to 4 weeks



Baseline demographic and functional characteristics of study subjects

	Control Group Mean (SD)	Experimental group Mean (SD)	P value
Age (years)	66.4 (6.8)	72.7 (9.9)	P=0.69
Gender (M/F)	4/4	7/5	
FEV_1	0.80 (0.25)	0.82 (0.45)	P=0.91
BMI (kg/m^2)	29.1 (11.2)	22.9 (6.2)	P=0.13

O_2 sats (%) resting	92.6 (3.2)	92.4 (3.9)	P=0.92
ISWT (metres) Baseline	10.0 (17.3)	20.9 (35.7)	P=0.47
Quads strength (Nms) baseline	170.9 (94.5)	109.4 (50.9)	P=0.79

Table 1

BMI= body mass index, Kg/m^2= kilograms per metre squared, O_2 sats= oxygen saturations, Nms= Newton metres.

The baseline characteristics are represented in table 1. There were no significant differences between the groups for the reported measures, on average the group has severe airways disease FEV_1 mean average of 30.4% GOLD group III to IV. There was a between group difference in the FEV_1 measurements of the control (0.80L) and experimental (0.82L) groups. The mean BMI for the group is 24.8 Kg/m^2, however the control group had a slightly higher BMI than the experimental group (29.1 compared to 22.9). Resting oxygen saturations were low for both groups. 6 patients out of the sample of 20 who were able to complete the ISWT at baseline, used supplemental oxygen of between 24-28%. The ISWT was very low for both groups. The difference between groups at baseline was not statistically significant. It was difficult to compare groups due to the small amount of data in the control group; therefore data will be explained by group.

Paired t-test data

Control group

Paired data	**Mean difference**	**SD**	**CI lower**	**CI upper**
ISWT baseline to ISWTm 4wks	105.0	117.3	-291.7 to	81.7
ISWT Discharge to ISWT 4wks	56.7	55.1	-281.3 to	254.6
ISWT baseline to ISWT 4wks	92.0	98.8	-214.7 to	30.7
SG baseline to SG discharge	118.6	52.6	-591.4 to	354.2
SG discharge to SG 4wks	0.6	18.9	-170.8 to	169.5
SG baseline to SG 4wks	37.5	104.6	-204.0 to	129.0

Table 2

Experimental group

Paired data	**Mean difference**	**SD**	**CI Lower**	**CI upper**
ISWTbaseline to ISWTdischarge	40.0	57.5	-81.7 to	1.2
ISWT discharge to ISWT 4wks	29.2	22.9	5.1 to	53.2
ISWT baseline to ISWT 4wks	55.6	67.3	-111.9 to	0.6
SG baseline to SG discharge	33.3	59.5	-79.0 to	12.5
SG discharge to SG 4wks	-22.0	36.1	-22.8 to	66.7
SG baseline to SG 4wks	9.1	15.5	-22.0 to	3.9

Table 3

Tables 2 and 3. SG=strain gauge in Newton metres ISWT= shuttle walk metres SD=standard deviation CI=confidence interval (95%) 4 wks follow up data.

Effect of NMES on muscle performance.

In-patient results

Experimental group

The data generated from strain gauge measurements of quadriceps strength was normally distributed. During the in-patient stay the maximum strength increased from 120.0 (SD 56.2)Nm to 153.1 (SD 73.4)Nm p=0.13 (df 8) (n=9) although this was not a significant increase (p>0.05) in quadriceps strength, equally there was no decline observed. From baseline to discharge from hospital there was a mean increase of 33.3 (SD 59.5)Nm (95%CI –79.0 to12.5).

Control group

Only a small number of patients completed the control period n=5, inevitably data analysis has been compromised, therefore results reported for the control group will reflect general trends. There was an increase in quadriceps strength during the in-patient period the mean increase was 118.6 (SD 52.6)Nm (95%CI –591.4 to 354.2).

Discharge to 4 weeks

Experimental group

From discharge to 4 weeks there was a mean decline of 22.0 (SD 36.1)Nm (95%CI –22.8 to 66.7). This was not statistically significant p>0.05.

Control group

There was a small increase in quadriceps strength from discharge to 4 weeks of 0.6 (SD18.9)Nm (95%CI –170.8 to 169.5) this was not statistically significant p=0.97.

Baseline to 4 weeks

Experimental group

Comparing the baseline data with the data collected after 4 weeks of NMES using a paired t-test, the maximum quadriceps strength had marginally improved in the experimental group. From baseline to 4 weeks there was a small mean increase of 9.1 (SD 15.5)Nm (CI –22.0 to 3.9), however The t test data in relation to quadriceps strength noted that Levene's test for equality of variances was not significant p>0.05, equality of means data also failed to generate p>0.05. (Raw data used for paired t test illustrated in table 2, raw strain gauge data shown in table 4).

Control group

The baseline mean quadriceps strength was 170.9 (SD 94.5)Nm increasing to 207.8 (SD 107.6)Nm p=0.526 (df 3), translating to an overall mean increase of 36.9Nm from baseline to 4 weeks. There were no significant increases in quadriceps strength using the paired t-test (fig 1) from baseline to 4 weeks mean increase 37.5 (SD 104.6)Nm (95%CI -204.0 to 129.0) p=0.53.

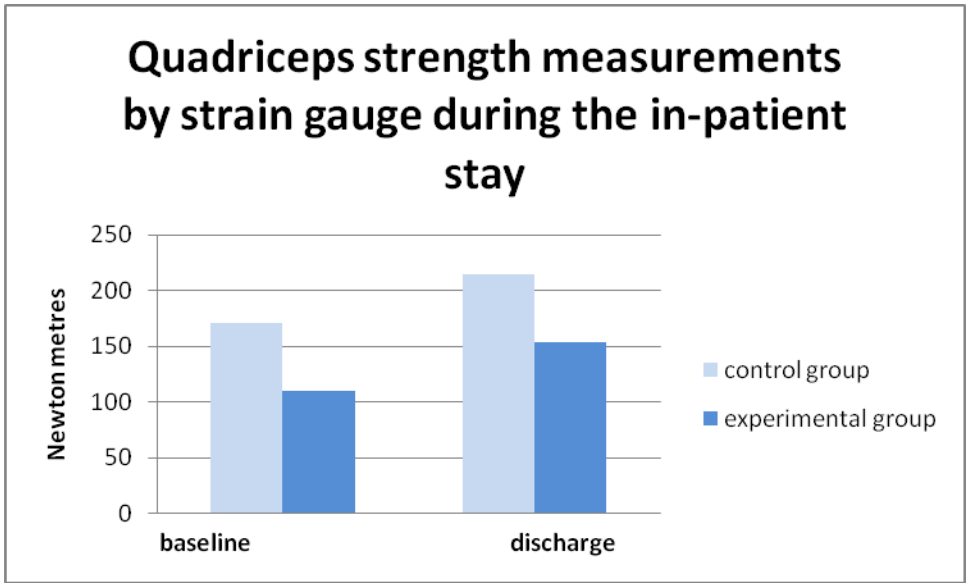


fig 1

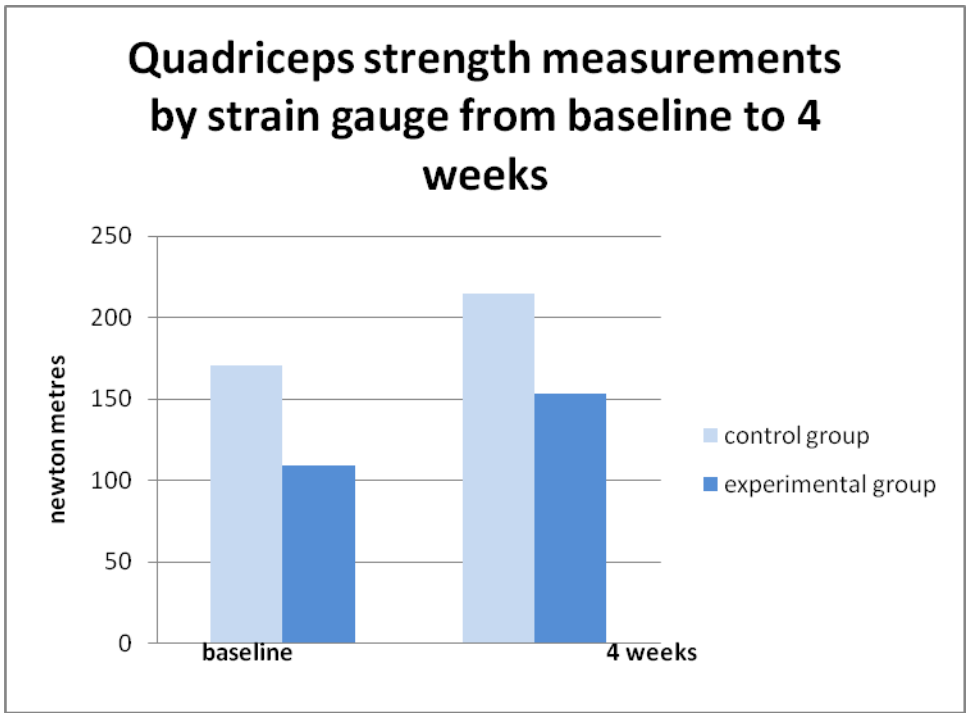


fig 2

Group comparison

Comparing the groups is difficult due to the small sample size in the control group. A repeated measures ANOVA noted that there was a significant difference dependent on treatment group $F(1.51)=10.10$ $p<0.5$, there was no time/group interaction. However these results cannot be definitively concluded upon due to the small sample size tested. Figures 3 and 4 illustrate each

patient's strain gauge measurements at the three time intervals; the missing data shows how difficult statistical analysis was.

	baseline	**Discharge**	**4 weeks**
Experimental	109.4 (SD50.9)	153.3(SD73.4)	91.5(SD37.9)
	n=13	n=9	n=8
Control	170.9(SD94.5)	214.9(SD124.3)	207.8(107.6)
	n=6	n=3	n=5

Table 4.

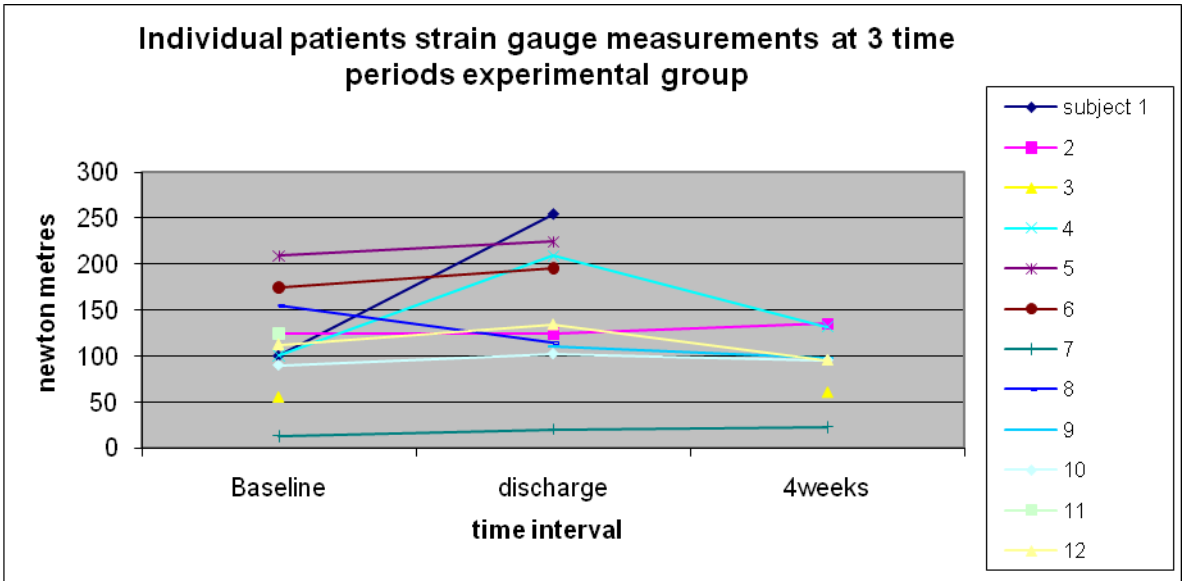


fig 3

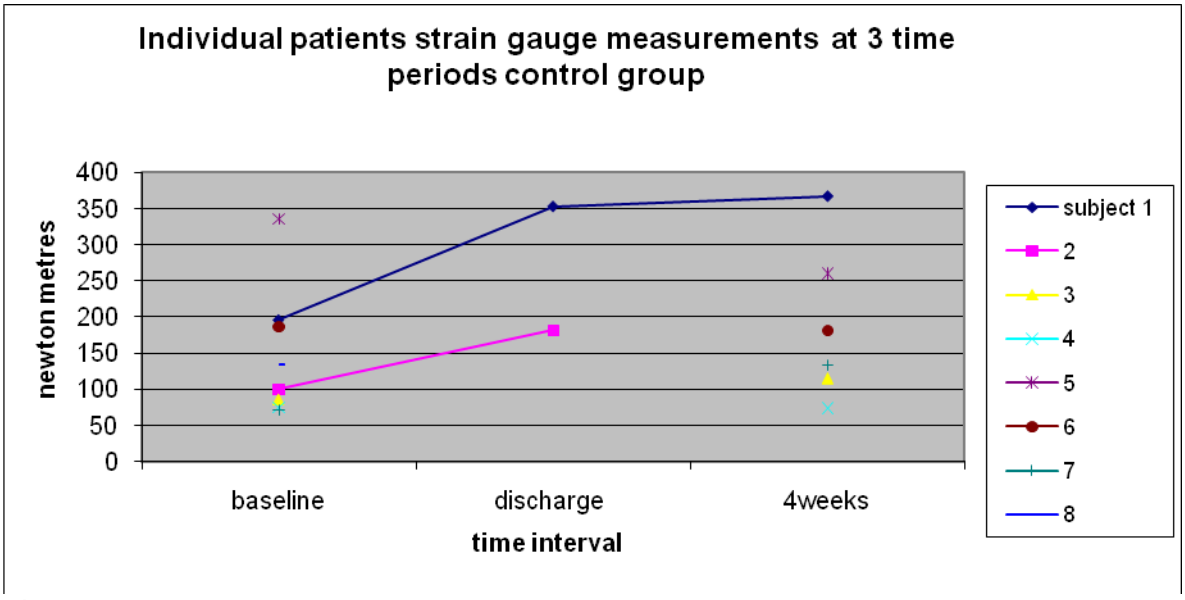


fig 4

Effect of NMES on exercise capacity

In-patient results

Experimental group

For the experimental group the mean baseline ISWT was 21.0 (n=8) (SD 37.8)m. On discharge from hospital the mean had increased to 61.0 (SD 49.0)m (mean increase 40m) (fig 5). Although the increases were not consistently statistically significant a paired samples t-test illustrated a strong trend towards improvement, as baseline to discharge mean increase 40.0m p=0.06 (df=9) (95%CI –81.7 to 1.1);

Control group

In the control group the baseline mean ISWT was 10.0 (n=5) (SD 20.0)m, at discharge the mean distance was 115.0 (SD 109.1)m (mean increase of 105m) (CI –291.7 to 81.7). A paired samples t-test found no significant increase in exercise capacity from baseline to discharge p=0.171 (df=3) (95%CI –291.7 to 81.7).

Discharge to 4 weeks

Experimental group

The increase in exercise capacity from discharge from hospital to 4 weeks was significant p=0.03 (df=5) (95%CI 5.1 to 53.2).

Control group

From discharge to 4 weeks the increase in ISWT was not significant p=0.850 (df=2) (95%CI -281.4 to 254.6).

Baseline to 4 weeks

Experimental group

At 4 weeks the mean had further improved to 70.6 (SD 60.1)m from baseline to 4 weeks) (fig 8). From baseline to 4 weeks mean increase 55.6m p=0.05 (df=7) (95%CI –111.9 to 0.6). The data was normally distributed apart from the baseline ISWT as there were several subjects unable to complete the test. Levene's test for equality of variance demonstrated p>0.05, the t test for equality of means also demonstrated p>0.05 in relation to ISWT data.

Control group

At 4 weeks the mean distance was 100.0 (SD 93.0)m (a mean increase of 90m from baseline to 4 weeks), from baseline to 4 weeks mean increase 92.0m p=0.11 (df=4) (95%CI –214.7 to 30.7). Individual patient data see fig 6.

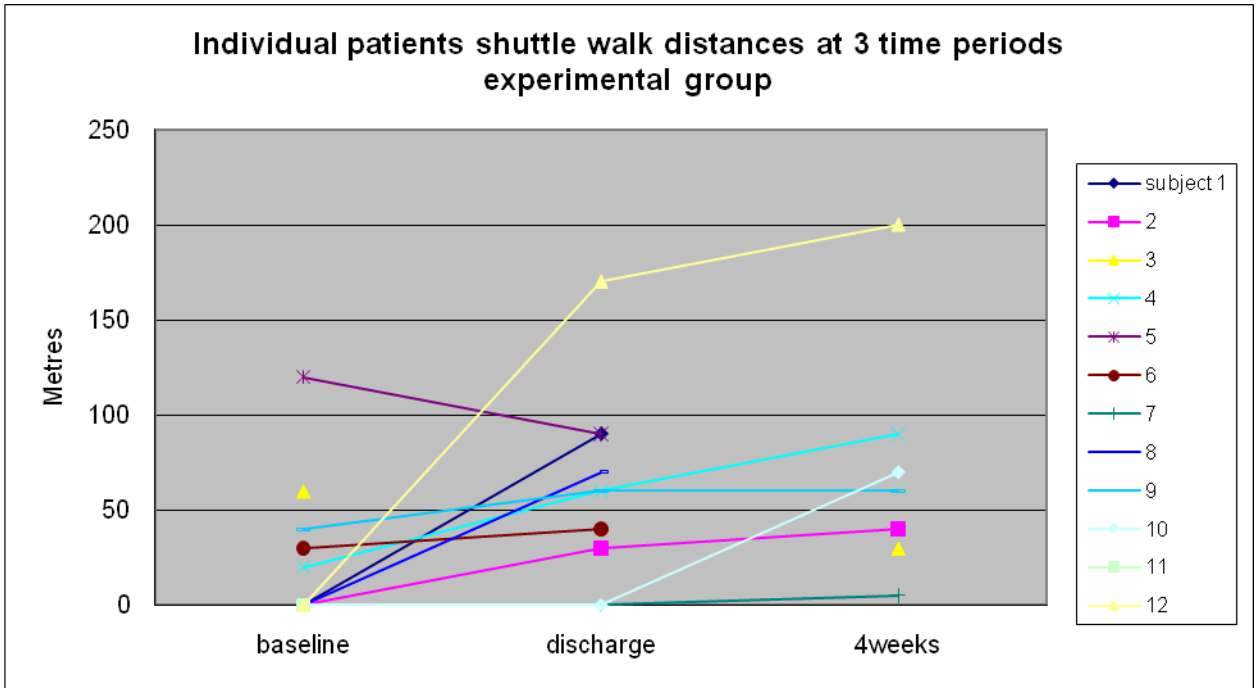


Fig 5.

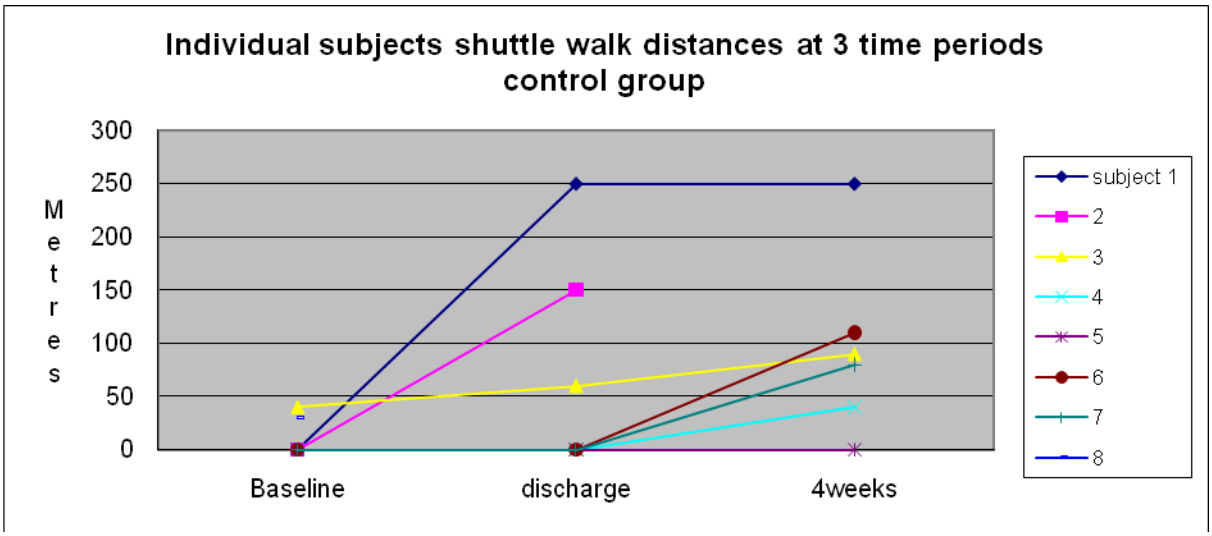


fig 6

Group comparison

A repeat measures ANOVA noted that between groups F=0.380 and this did not generate a level statistical significance p>0.05. Again it is difficult to make any firm conclusions from this data due to the small sample represented. For the effect of time F=5.137 therefore the effect of time was not statistically significant. (Raw ISWT data shown in table 5).

	Baseline	**discharge**	**4 weeks**
Control	10.0(SD17.3)	115.0(SD109.2)	100.0(SD93.0)
	n=7	n=4	n=5
experimental	20.8(SD35.8)	61.0(49.1)	70.6(SD60.1)
	n=13	n=10	n=8

Table 5

Figures 5 and 6 illustrate each subjects shuttle walk tests results at each of the time intervals, again the lack of data makes it difficult to analyse and draw meaningful conclusions from.

Effect of NMES on activity

For the first 4 days of the study patients were asked to wear an activity monitor. Overall there was a trend for recorded activity to decline independently of any intervention. An independent samples t-test found no significant difference in number of steps taken between the control and experimental groups. On day 1 the mean number of steps taken for the experimental group were 530 (SD 609.3), the control group took 634 (SD 494.4) steps. By day 4 the experimental group had taken a mean number of 423 (SD 623.3) steps, whereas the control group took 447 (SD 441.2) steps.

Day 1-4 comparison

An independent samples t-test of the number of steps taken found that for day one p=0.812 df=6; by day five p=0.753 df=3. This illustrated no statistically significant difference. (fig 7 demonstrates number of steps against days, experimental group n=5 control group n=3).

A repeat measures test also found no significant difference in number of steps taken within the groups. For the control group for days 1 to 4 p=0.62 (df=1) (n=2). For the experimental group for days 1 to 4 p=0.38 (df=3) (n=4). For the t-tests the data up to day 4 was used only as by day 5 n=1 in the control group. A Pearson correlation also found no relationship between baseline ISWT distances and the number of steps taken in the first three days the activity monitors were worn, day p=0.23, day 2 p=0.28 and day 3 p=0.68.

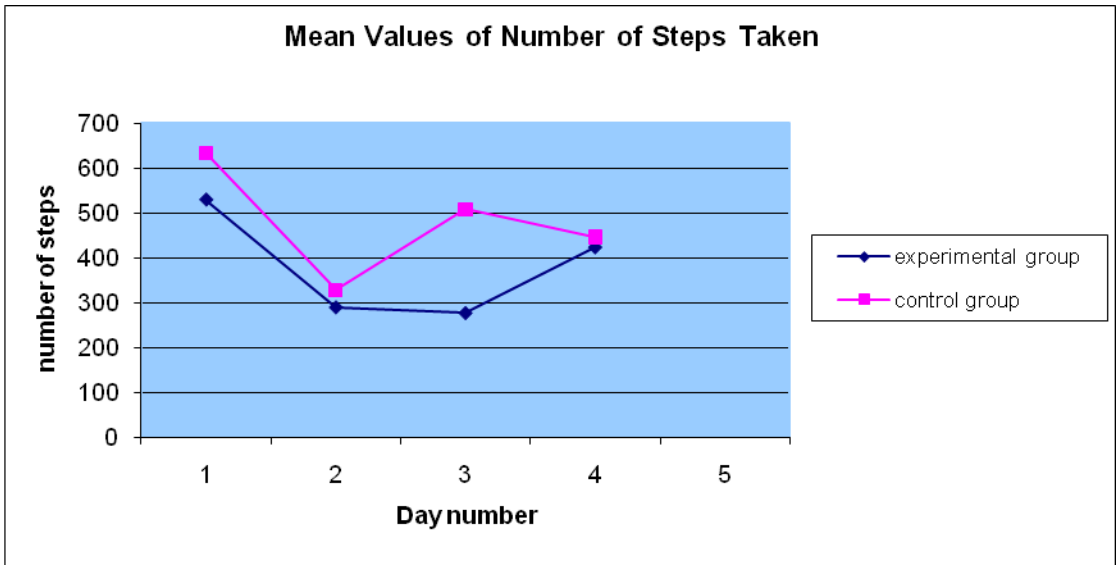


fig 7.

Effect of NMES on anxiety and depression (HADS scores).

Experimental group

Anxiety and depression data was collected at baseline and 4 weeks only. The mean depression score at baseline was 8.3 (SD 3.9). The mean anxiety score at baseline was 11.0 (SD 4.1). At 4 weeks the mean anxiety score was 10.3 (SD 3.0) and the mean depression score was 7.9 (SD=2.0). A Wilcoxon Signed Ranks Test found no significant difference in HADS scores, (anxiety p=0.311, depression p=0.550) (fig 8).

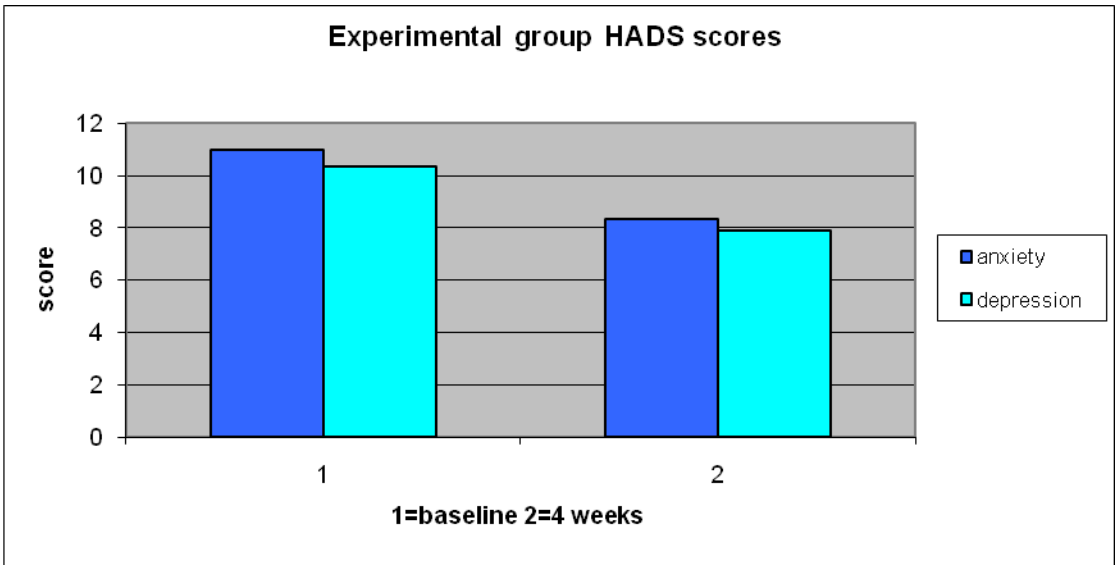


fig 8.

Control group

For the HADS questionnaire the mean anxiety score in the control group at baseline was 10.7 (SD 4.3), and the mean depression score was 7.8 (SD 2.0). At 4 weeks the mean anxiety score was 9.8 (SD 4.8). The mean depression score was 8.5 (SD 3.5). A Wilcoxon Signed Ranks Test found no significant difference in the HADS scores of the control group (anxiety p=0.10) (depression p=0.66). Therefore there was no significant difference in the levels of anxiety and depression in the control group from baseline to 4 weeks (scores illustrated in fig 9).

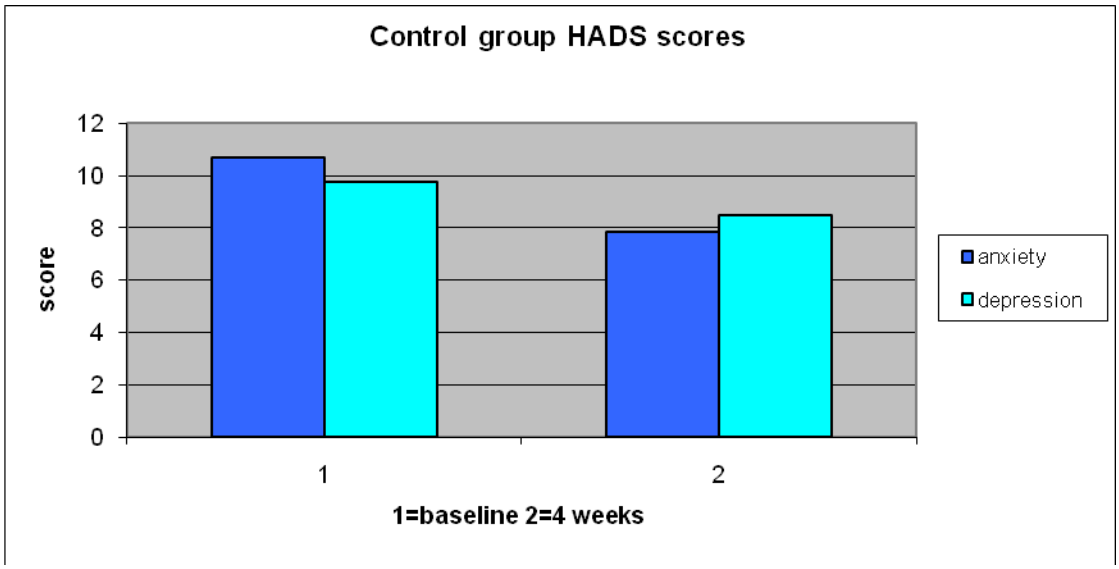


fig 9.

Group comparison

A Friedman test found no significant differences in HADS scores between the control and experimental groups. For the anxiety scores p=0.32, and for the anxiety group p=1.0.

Health related quality of life (CRQ-SR) data.

Experimental group

In the experimental group at baseline the mean dyspnoea score was 2.3 (SD 1.3), the mean fatigue score was 2.8 (SD 1.0), the mean emotion score was 3.5 (SD 1.2), and the mean mastery score was 3.3 (SD 1.3). At 4 weeks the mean dyspnoea score was 2.9 (SD 1.3), the mean fatigue score was 2.8 (SD 1.3), the mean emotion score was 3.7 (SD 1.2) and the mean mastery score was 4.2 (SD 1.1).

A Wilcoxon Signed Ranks Test noted that there was no statistically significant increase in score over the 4 week period; (dyspnoea p=0.61, fatigue p=0.95, emotion p=0.44, mastery p=0.11). Therefore there were no significant increases in health related quality of life over the 4 week trial period, however some clinically significant results were gained, where scores increased by 0.5 mastery domain (fig 8).

Control group

The mean scores in the dyspnoea domain at baseline was 2.3 (SD 0.6), the mean fatigue score was 2.1 (SD 0.5), the emotion score was 3.1 (SD 0.4) and the mastery score was 3.1 (SD 1.1). At 4 weeks the mean dyspnoea score was 2.6 (SD 0.2), the fatigue score was 2.6 (SD 0.8), the emotion score was 3.6 (SD 1.1) and the mean mastery score was 3.5 (SD 1.5). There was no significant difference in any of the four domains (dyspnoea p=1.00, fatigue p=0.13, emotion p=0.23, mastery p=0.23). However there were clinically significant improvements in the fatigue, emotion and mastery domains (scores illustrated in fig 10 and fig 11, changes in table 6).

Paired samples Mean changes in CRQ results from baseline to 4 weeks

	Dyspnoea	Fatigue	Emotion	Mastery
Experimental	-0.3	0.2	-0.1	-0.8
N=8	(SD1.9)	(SD1.5)	(SD1.1)	(SD1.2)
	CI-2.1 to 1.4	CI-0.9 to1.3	CI-1.0 to 0.7	CI-1.7 to 0.2
Control	-0.3	-0.7	-0.7	-0.4
N=5	(SD0.8)	(SD0.9)	(SD1.1)	(SD0.8)
	CI-2. to 1.7	CI-1.8 to 0.5	CI-2.1 to 0.7	CI-1.4 to 0.6

Table 6

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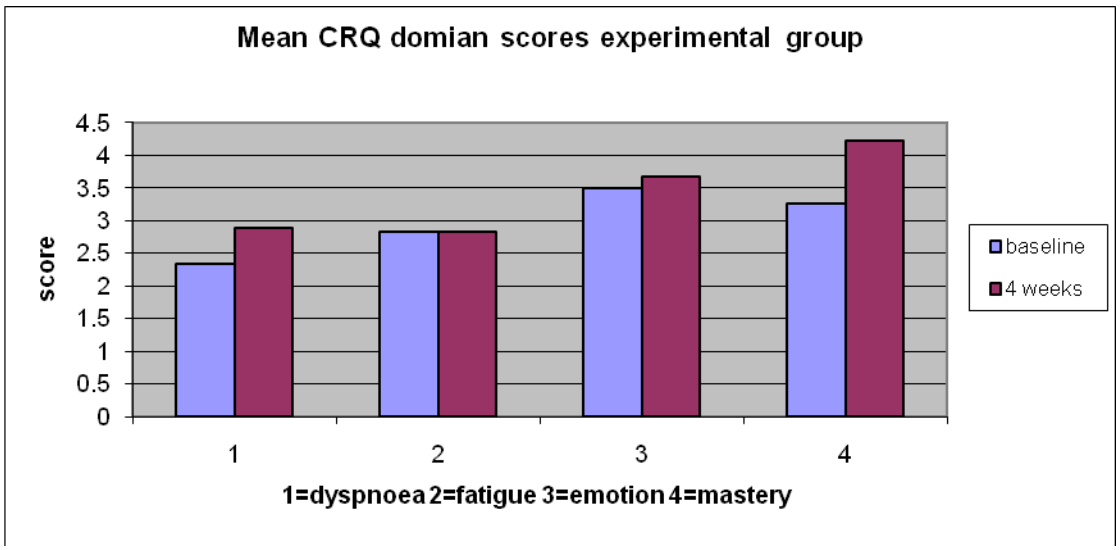

fig 10.

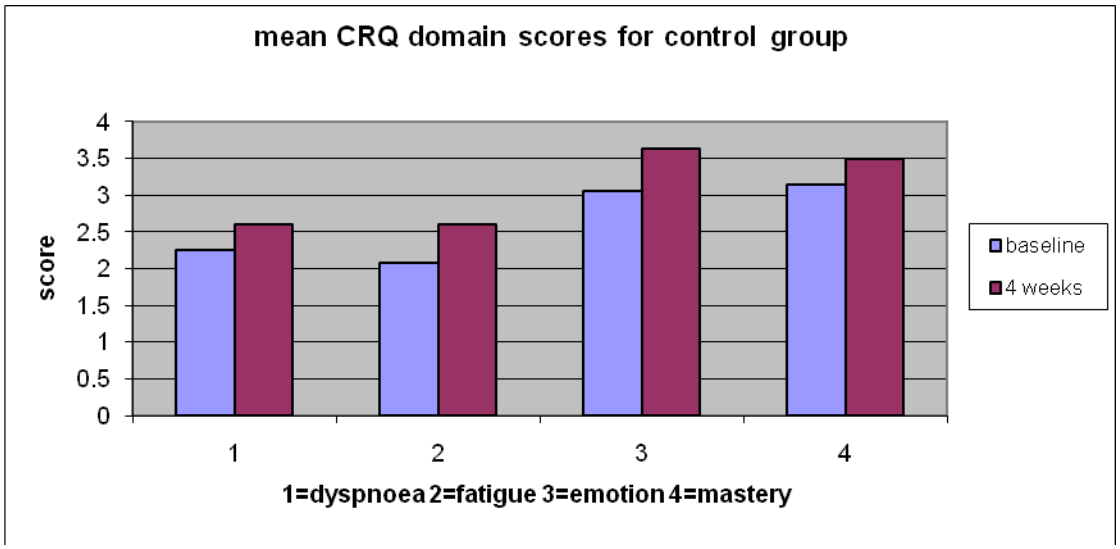

fig 11.

Group comparison

A Friedman test generated statistically significant results in the emotion domain only (p=0.03) , this could be a type 1 error. In the dyspnoea domain p=0.53, p=0.29 in the fatigue domain and p=0.11 in the mastery domain.

Effect on MRC and Borg scoring

Experimental group

Mean MRC at baseline was 4.8(SD 0.6), mean MRC at 4 week follow up was 4.7 (SD 0.7). A Wilcoxon signed ranks test found no significance between the experimental groups MRC scores from baseline to 4 weeks (p=1.00)

The mean resting Borg score for the experimental group at baseline was 2.4 (SD 1.2) at 4 weeks the mean was 1.0 (SD 1.0). There was no significant improvements in resting Borg score (p=0.32).

The mean Borg breathlessness at baseline was 3.9 (SD 0.7) at 4 weeks the mean was 3.8 (SD 0.8). There was no significant difference in the

breathlessness scores; following ISWT from baseline to 4 weeks p=1.00. The mean Borg exertion score at baseline was 9.1 (SD 6.2), at 4 weeks the mean was 13.0 (SD 4.0). At the end of 4 weeks there was no significant improvement in Borg exertion scores p=0.37.

Control group

At baseline the resting mean Borg score was 1.6 (SD 1.8) at 4 weeks the mean was 3.0 (SD 2.8). A Wilcoxon signed ranks test found no significant improvement in scores (p=0.66)

The baseline mean Borg breathlessness score was 2.5 (SD 0.7), at 4 weeks the mean was 4.3 (SD 0.6). The mean Borg exertion score at baseline was 8.8 (SD 11.7), at 4 weeks it was 14.0 (SD 1.0). There was no significant improvement for either group in perceived breathlessness or perceived exertion (results illustrated in fig 12 and fig 13).

At the beginning of the trial the mean MRC was 4.6 (SD 1.1) at 4 weeks the mean was 3.8 (SD 0.8). There was no significant improvement in MRC scores from baseline to 4 weeks p=0.33.

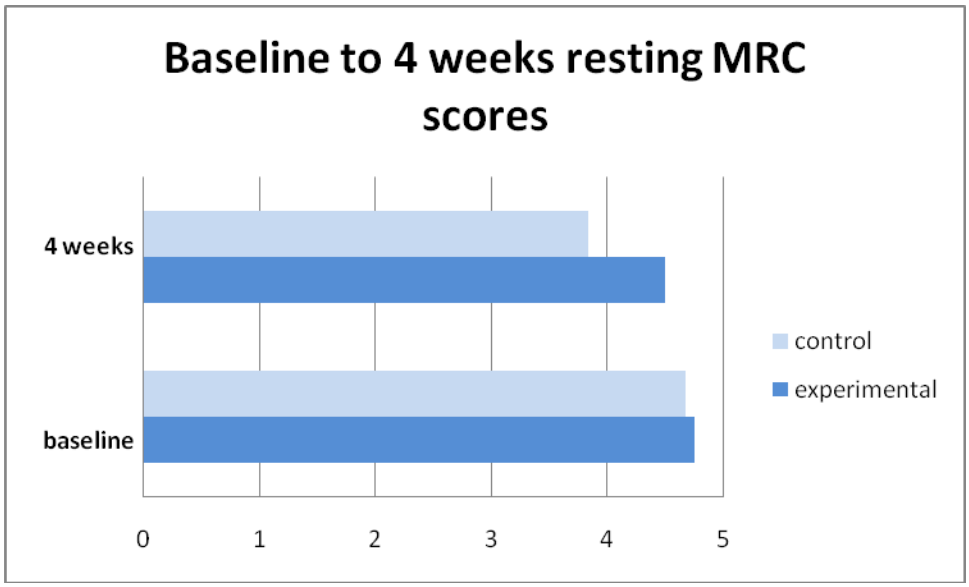
Baseline to 4 weeks resting MRC scores
4 weeks
baseline
0
1
2
3
4
5
control
experimental

fig 12.

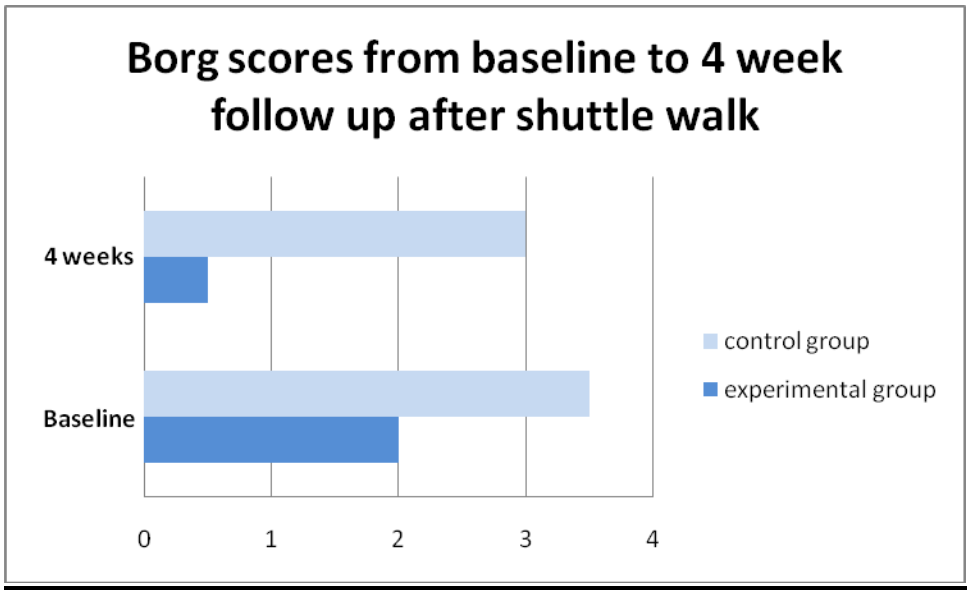
Borg scores from baseline to 4 week follow up after shuttle walk
4 weeks
Baseline
0
1
2
3
4
control group
experimental group

fig 13

Discussion

This is the first study to describe the effects of NMES during an acute exacerbation of COPD. It was delivered within the context of an established Active Therapy Unit, which has been set up within the Pulmonary Rehabilitation department at Glenfield Hospital, University Hospitals Leicester NHS Trust.

The main findings of the study were that there were no baseline differences between the control and experimental groups. There was also no between groups differences in the level of activity taken. Throughout the trial period there was an increase of 9.1 (SD15.5)Nm in quadriceps strength. However the control group also demonstrated an increase in quadriceps strength (37.5 SD104.6)Nm. Neither of these increases generated a level of statistical significance. Exercise performance as measured by ISWT was improved for both groups over the 4 week period. For the experimental group the mean distance walked at discharge from hospital was 61.0 (SD49.0)m, from discharge to 4 weeks there was a small significant increase to 70.6 (SD60.1)m p=0.026. Distances covered in the ISWT by the control group were also improved. The mean distance at discharge was 115.0 (SD109.1)m there was then a small decrease at 4 week follow-up (100.0 SD93.0)m. No statistically significant improvements in health related quality of life were observed. There were clinically significant improvements noted in the mastery domain of the CRQ-SR.

The problems with recruitment in the current study make it difficult to draw any firm conclusions from the control group data. Therefore this discussion will incorporate the control group data but mainly focus on the results of the intervention group. Overall this current study noted that by encouraging patients to walk and by using NMES quadriceps strength was not only maintained, but also improved and ISWT results also illustrated a strong trend towards improvement.

The ATS/ERS (2006) state that pulmonary rehabilitation has been recognised as a cornerstone in the management of COPD patients. However they note that further research is required to optimise the effectiveness of rehabilitation, this includes defining the effects of the non-volitional components of rehabilitation; for example hormonal therapies and supplemental oxygen. NMES could be considered one of these strategies that may be a particularly important adjunct to rehabilitation during an acute exacerbation where patients have ventilatory limitations.

Two previous papers by Spruit *et al* (2003) and Pitta *et al* (2006) have identified a decline in physical performance during an acute exacerbation. Both papers reported a decline in quadriceps force during hospitalisation. Both groups in this current study appeared to benefit from some intervention. The experimental group had an active stimulation profile and supervised walking, whilst the control group had a sham NMES intervention plus supervised walks, or pedals. This is an important difference between the current study and those reported by Spruit *et al* (2003) and Pitta *et al* (2006)

where no intervention was offered. Pitta *et al* (2006) noted a positive correlation between time spent in weight bearing activity and quadriceps force at day 8 of hospital admission. Therefore it would appear that any modest form of activity may be of value to the individual in preserving quadriceps strength during the acute phase of an acute exacerbation.

Muscle strength

NMES can be used to improve the fundamental properties of muscles. Previous research has found that NMES can be of use as an adjuvant therapy for COPD patients during stable disease. In comparison to previous studies utilising NMES was quite difficult as it was used in an acute setting where using NMES was not an established therapy in COPD. A study by Bourjeily-Habr *et al* (2002) conducted research using NMES they found that after 6 weeks of NMES that quadriceps strength had improved significantly in the treatment group from (44.7 (6.5) to 55.2 (6.6) Nm p=0.004). The current study noted a mean increase in quadriceps strength from baseline to discharge from hospital of 33.3 (SD 59.5)Nm (95%CI –79.0 to 12.5) but this was not a statistically significant increase (p>0.05). The control group also demonstrated a non statistically significant increase in quadriceps strength during the in-patient stay, mean increase 118.6 (SD 52.6)Nm (95%CI -591.4 to 354.2) perhaps more importantly a significant decline in function was not detected.

The study by Neder *et al* (2002) also noted trends towards improvement in quadriceps force following NMES, however these improvements were not significant, (from 64.4 (32.3) to 91.8 (29.3)Nm), again these measurements

appear to be very low compared to the current study, this could possibly be due to how disabled their sample was (mean predicted FEV_1 38.0-39.5%), although this could be related to the measurement technique used. Zanotti *et al* (2003) used a sample of patients in intensive care, their sample undertook active limb mobilisation with or without NMES, they found that after 28 days both groups illustrated significant increases in muscle strength, the group that also used NMES was able to further increase that strength (from 2.16 ±1.02 vs 1.25±0.75, p=0.02 using muscle strength scoring system 0-5). They illustrated a decrease in the number of days needed to transfer from bed to chair (10.75 ± 2.41 days vs 14.33 ± 2.53 days for the group who did, and did not respectively use NMES p=0.001) Although the patients in this current study were not in intensive care there is comparison to be made, as patients in this study were hospitalised for an average of 7-10 days which is as long as was needed to progress towards transferring from bed to chair, this decrease in time taken to transfer from bed to chair also correlates with the increase in quadriceps strength reported during the patients in hospital stay. It is however difficult to directly compare these favourable results to this study as muscle strength was calculated using a scoring system as opposed to using objective operator resistance measurement.

The sample taken by Vivodtzev *et al* (2006) were the most comparable to the sample used for this study in terms of disability, as the mean predicted FEV_1 was 30±3% (30.4% for this particular study). Vivodtzev *et al* (2006) reported that in their study at 4 weeks both the control and treatment groups displayed a significant increase in maximal volitional contraction of the quadriceps, since

both groups were undertaking traditional rehabilitation. In the rehabilitation plus NMES group there was a 35% increase in maximum volitional contraction (97±71 contractions while seated on a dynamometer), in the control group there was an increase of 14% (36±34 contractions) p=0.03. Vivodtzev *et al* (2006) found significant improvements in quadriceps strength, and significant improvements in the 6-minute walking test. This current study is broadly in line with their findings, noting improvements in quadriceps strength but these were not significant, and ISWT increases which displayed a trend towards significance.

Dal Corso *et al* (2007) recruited a population that is the most diverse to the current study, and found no significant increases in quadriceps strength (93.8±43.7 to 103.2±50.6Nm) following 6 weeks NMES. This population were in relatively good health therefore less improvement might be achieved by involuntary training, voluntary training alone may have been more beneficial.

It could have therefore been hypothesised that this current study would potentially secure significant increases in quadriceps strength as the sample were all severely impaired and suffering exacerbation, however the results do not illustrate this; reasons for this are most likely due to the small sample size used, and the fact that the control group did not have imposed bed rest, and were encouraged to mobilise; or possibly that the NMES was effective in the period from baseline to discharge from hospital but then improvement during the ‘home period’ was not as pronounced. This current study incorporated the use of diary cards in order to monitor compliance and improve motivation;

however analysis of the data was beyond the scope of the study. Although not all patients completed these cards and it is difficult to assess the accuracy of these as their completion during the study was not monitored.

Exercise Capacity

In terms of exercise capacity the experimental group did not illustrate statistically significant improvements over the 4-week period, however in the period from discharge from hospital to 4 weeks the improvement was statistically significant. It is however worth noting this statistical significance with caution, as it could be attributed to a type I error, as an assumption can be made that since so many statistical tests were conducted there is a chance one will reach a significant level. Boujeily-Habr *et al* (2002) noted a significant increase in physical capacity (p=0.007) the mean shuttle walk distances increased from 185.2 (21.8)m to 254.4 (30.4)m. Whereas for this study at baseline the mean distance was 21.0 (37.8)m which increased to 70.6 (60.1)m at 4 weeks. For the control group for the same period the mean baseline was 10.0 (20.0)m increasing to 100.0 (93.0)m at four weeks. Direct comparisons cannot be made as the groups in the current study and Bourjeily- Habr *et al* (2002) study were not similarly disabled. Natural recovery from exacerbation was also not accounted for.

Man *et al* (2004) recruited a sample of 42 patients admitted to hospital with an acute exacerbation. They were randomised into either an early rehabilitation group (within 10 days of discharge) or allocated into a usual care group. 24 hours prior to discharge patients completed an ISWT. At discharge the

median ISWT for the usual treatment group was 115m and for the early rehabilitation group it was 120m. However when patients were reviewed at 3 months post discharge the ISWT distances were 90 and 210m respectively. Man *et al* (2004) concluded that the patients who attended rehabilitation within 10 days of discharge from hospital displayed clinically significant improvements in exercise capacity and health status at 3 months. This translated into 35.0% versus 57.1% readmission rate for the early rehabilitation group with fewer in-hospital days.

The current study demonstrated overall increases in ISWT distances up to 4 weeks despite a mean decline of 12m from discharge to 4 weeks for the control group. This would seem to support the idea that early intervention is of benefit since even the control group did not remain completely sedentary. The argument remains what is the best form of intervention whether it be NMES or early pulmonary rehabilitation would require further research. The pattern of ISWT performance appears to be similar between the current study and that of Man *et al* (2004). Seemungal *et al* (2000) note that in their study of recovery following exacerbation, that peak expiratory flow rate was only recovered to baseline in 75.2% of patients at 35 days, for 7.1% of patients recovery to baseline had not occurred by 91 days. However this cohort of patients were all attending outpatients clinics but were not partaking in rehabilitation, this appears to illustrate natural recovery from exacerbation.

Neder *et al* (2002) noted significantly higher exercise tolerance following NMES ($p<0.01$), although the exercise taken cannot be directly compared as

a cycle ergometer was used as opposed to the ISWT. A significant increase in 6 minute walking distance (63±40m, p=0.01) was found for the experimental group by Vivodtzev *et al* (2006). The control group reported by Vivodtzev *et al* (2006) also displayed an increase in distance although it was not significant (increase of 30±38m p=0.07). These improvements could be attributed to the fact that both the experimental and control groups also undertook usual rehabilitation.

Dal Corso *et al* (2007) found that NMES had no significant effect on 6 minute walking distances. One of their main findings noted that NMES had no discernable effect on muscle strength or walking capacity, although there were fibre changes at micro-structural levels. One reason that their findings did not concur with the aforementioned studies could be attributed to the sample used, as the sample taken by Dal Corso *et al* (2007) were all outpatients with mean predicted FEV_1 measurements of 49.6±13.4%; compared with the current study whose experimental mean FEV_1 predicted was 30.5 (SD 13.1)%, which although makes them moderately impaired means they were not as debilitated as the samples used in this research or the other papers reviewed.

Quality of life

This study found no significant difference in anxiety and depression levels at 4 weeks following NMES; it also found that although there were no significant differences in CRQ data there were some clinically significant results. This is in comparison with the findings of Spencer and Jones (2003) who reported

significant improvements in the SGRQ at 4 weeks following exacerbation, and reported further improvements between 4-12 weeks. Man *et al* (2004) note that at 3 months following exacerbation there were significant improvements in all four domains of the CRQ for the early rehabilitation group. Therefore if the CRQ was repeated again from 4-12 weeks there may have been a significant improvement noted, or if the rehabilitation period had been extended.

Voll-Aanerud *et al* (2008) suggest that respiratory symptoms such as cough, dyspnoea and wheeze are more strongly associated with Health Related Quality of Life (HRQL) than pulmonary function. Therefore if this study had also looked at differences in respiratory symptoms in conjunction with the CRQ there may have been a more representative change in HRQL. Neder *et al* (2002) found that following NMES mean scores for the dyspnoea domain of the CRQ had improved compared with baseline (mean difference 1.4 (95% CI to 2.3); $p<0.05$). To assess HRQL Vivodtzev *et al* (2006) utilised the 28 item Maugeri Foundation Respiratory Failure Questionnaire (MRF-28). Despite this differing from the CRQ, it is comparable because like the CRQ it is disease specific and self-administered. After assessment using the MRF-28 Vivodtzev *et al* (2006) noted a significant decrease in the 'dyspnoea in daily activities domain' in the NMES group. This supports the clinically significant changes noted in this current study. This current study did not continually supervise patients once they were familiar with the NMES unit, however if patients had been more closely supervised or possibly always had a health professional to walk with them during the trial, or a home visit it could be speculated that

there could have been larger improvements in HRQL, although this would be time consuming for the research team.

Bourjeily-Habr *et al* (2002) note a significant improvement in their experimental groups perceived exertion level from (12.7 (SD 0.64) to 10.1 (SD 0.90) p=0.01), this differed from their control group whose improvement was not significant (12.8 (SD 0.88) to 12.6 (SD 0.76) p=0.79). In comparison Vivodtzev *et al* (2006) recorded their samples Borg dyspnoea scores for the experimental group, the pre treatment score was 6.5±2.3 and post 6.0±1.5 this was not a significant improvement (p=0.39). In their control group the mean score was 5.0±2.9 and the post score was 6.0±2.6 (p=0.07), this is interesting as neither were statistically significant however both groups in the study by Vivodtzev *et al* (2006) took part in usual rehabilitation which did not significantly improve their dyspnoea or perceived exertion; despite this the authors reported that the experimental group reported improvements in their dyspnoea after completing health related quality of life questionnaires.

The results in the current study illustrated no significant improvements in either the control or treatment groups' perceived dyspnoea as measured by the MRC and Borg scores. It was also confirmed that there were no significant improvements in the patients' perceived breathlessness or exertion from baseline to 4 weeks, for either the control or treatment groups.

Current study findings

The findings of this current study do not necessarily reiterate the improvements in physical performance following NMES described by previous studies. However the hypothesis was not that patients would improve; but rather that physical capacity be maintained during an exacerbation. Patients used in this sample were chosen if admitted with an exacerbation. However in previous research patients were chosen in the absence of exacerbation. Only the study by Vivodtzev *et al* (2006) incorporated a sample of similarly disabled patients, although they were all recovering from exacerbation. This study did illustrate that physical capacity can be maintained during an exacerbation. It is difficult to attribute this maintenance solely to the NMES because the control group did not remain completely sedentary. In the clinical environment it is unethical to say to the experimental group that they must not undertake any physical exercise because it is widely known that physical activity is of benefit, although its benefit at the time of exacerbation is not known. Both groups were advised to complete a supervised walk each day as long as was tolerated; walking is aerobic activity which is not necessarily associated with an increase in quadriceps strength. If walking was declined pedals for use at the bedside were offered as an alternative. Therefore this study is unable to detect if any maintenance or improvement in physical capacity is due to the NMES protocol, or rather the provision of any type of intervention during the occurrence of exacerbation.

Physical capacity

Pitta *et al* (2006) note that patients with a low activity level at one month following discharge were more likely to be readmitted during the year, this correlates with the time course of most NMES studies, which range from 4 to 8 weeks. The sample of patients investigated in the Pitta *et al* (2006) paper were similarly disabled to those in the current study (mean FEV_1 29-34% from day 3 of exacerbation to 1 month after). They found that patients had a low level of physical activity during and after hospitalisation, and that during the course of an 8 day in-patient period there was a significant reduction in quadriceps force (Nm98-90 day 3-8) of exacerbation . In contrast the current study noted the same low level of physical activity but not the significant decline in quadriceps force. If patient management aimed to encourage physical activity for this period whether NMES was incorporated or not readmission rates may decline, however a structured period of an intervention such as NMES may ensure patient compliance for up to a month following discharge.

A further study by Pitta *et al* (2008) reiterated their previous findings by noting that during a 6-month rehabilitation programme after 3 months there were improvements in physical capacity, muscle force and functional status ($p<0.05$) reinforcing the need for promotion of physical activity. A Pearson correlation of the current study findings noted no significant correlation between number of steps taken in days 1-3 of admission and the distances in the baseline ISWT. Therefore if an intervention commenced early enough the baseline ISWT performance may be positively influenced.

From the data collected from the activity monitors it is clear that the sample of patients in this study were very inactive, despite the monitors being very sensitive to any movement. One reason for this could be patients assuming the sick role when admitted, or not receiving enough information about the benefits of exercise. Further research could aim to find out if there is a correlation between HADS and CRQ scores and levels of activity, this could provide clues as to what are the barriers preventing patients partaking in physical activity. The use of walking aids such as 'rollators' may also affect the number of steps taken by patients, as their results were so low. It is possible that the activity monitors were not sufficiently sensitive to register the movement of the patients when their arms were static holding on the rollator.

Limitations

This pilot study demonstrates it is feasible to employ NMES technology but there have been several difficulties with the study. As illustrated by previous studies of this nature the major limitation of this study is its small sample size, which means statistical results achieved lack the power to evaluate just how beneficial NMES could be. Recruitment could be improved by educating staff to the potential benefits of NMES, however there will always be reluctance as patients are aware that they may be in a control group not using a therapeutic technique. When undertaking research in a small unit recruitment can be hampered by patients taking part in other research trials. More robust results should be gained from the wider study that is in progress incorporating a larger sample. Another limitation is the fact that efficacy cannot be solely

attributed to NMES because it would be unethical to advise the experimental group not to undertake any physical activity during the trial period.

If NMES was incorporated into rehabilitation an analysis of cost effectiveness would need to be undertaken, it does however seem feasible to suggest that if a 4 week period of NMES can assist in preventing subsequent readmission to hospital then it would be worth it; not only financially but in terms of quality of life for the patient. Garcia-Aymerich *et al* (2003) suggested that there is an association between physical activity and a reduced readmission to hospital following COPD exacerbation, and that this has potential ramifications for rehabilitation and its adjuvant therapies. Since patients hospitalised with an exacerbation are so inactive during admission and after discharge from hospital, efforts to enhance activity at this time should be an aim of the disease management of COPD (Pitta *et al* 2006).

As previously mentioned it is also difficult to make this trial completely controlled as it would be unethical to expect patients to remain bed bound for the duration of the trial to allow any improvements in the treatment group to be attributed to the NMES, although this is standard practice in many wards across the UK. There are however encouraging results to be gained from the organisation of active therapy units where it is customary to offer physical therapy advice. It was also difficult to design a protocol for the control group, it would seem valid to use NMES settings for both groups but advise the control group not to touch the controls to increase the intensity, however if for example there were members of each group in close proximity to each other

in the ward and they talked about using the NMES unit, different instructions for usage may cause confusion or make it obvious which group they were in.

Another limitation noted by this study was that once discharged from hospital it became difficult to persuade patients to return for follow up, this would not have been such a problem if it was a clinic appointment and patients were going to be assessed by medical staff; there seemed to be less incentive to return to hospital to carry out physical assessment solely for research purposes.

The major limitation of this study is the small sample size and the heterogeneity of individual results, of the twenty patients recruited (ten in each group) only thirteen completed the 4-week trial, and due to this the statistical power was not sufficient to reveal the full benefits of NMES. These benefits may become apparent after the full trial of forty has been completed. This trial could almost be viewed as an investigation into how feasible NMES is in practice, or a pilot study preceding the wider study.

Further research

Although research has advocated the use of NMES as an adjuvant therapy in pulmonary rehabilitation its efficacy during periods of exacerbation has yet to rigorously tested, although some of the results of this study are promising there remains much research to be conducted. One such avenue could be the

metabolic response at muscle level to NMES during an exacerbation, which potentially could prove detrimental by increasing inflammation.

COPD patients exhibit signs of systemic inflammation, elevated levels of circulating catecholamines, increased sympathetic activation and muscle wasting at rest, it could be expected that physical activity will further increase these mediators (Van Helvoort *et al* 2005). However their study found that although exercise did enhance systemic inflammation, it was not exaggerated compared to healthy subjects, inflammation just occurred at a higher level and at a lower workload. It is worth noting that their sample were free from exacerbation for at least two months before commencing the trial.
Spruit *et al* (2003) note that during an exacerbation changes in metabolic, oxidative, nutritional and inflammatory state occurred, and in addition to steroid treatment and bed rest may result in a rapid decrease in muscle force. However a study conducted by Sillen *et al* (2008) found that when compared to resistance training NMES produced a significantly lower metabolic response; they also iterated that their study did contain some methodological limitations, which may limit validity. Spruit *et al* (2007) elucidate this by suggesting that high intensity cycling did increase levels of circulating inflammatory markers. Although the sample studied were hospitalised they were all clinically stable.

Another measurement that was not taken in this study, which could provide additional information, is quadriceps cross-sectional area. Marquis *et al* (2002) suggest that in a cohort of patients that they studied cross-sectional

area was a better predictor of mortality than BMI when FEV_1 <50%. They found that the combination of low predicted FEV_1 and cross-sectional area <70cm^2 led to a rise of 13.16 (CI 95% 1.74 to 99.20) in the mortality odds ratio. This could also be used as criteria for targeting the patients most in need of rehabilitation or NMES.

Further studies could also look at using different NMES protocols or one leg studies to ascertain which is the most beneficial as there are differences between those used in previous research. Vivodtzev *et al* (2008) define high frequency NMES as ≥50hz, and that frequencies of 50-120hz lead to significant improvements. Different frequencies could be explored. As well as different frequencies different duty cycles (on/off times) could be investigated. Higher frequencies combined with shorter duty cycles can result in increased muscle fatigue, however if larger electrode pads are used patient tolerance and quadriceps peak torque can be increased (Lyons *et al* 2005).

This study was also restricted by its limited use of activity monitoring. It appears that some activity monitors can differentiate between prescribed walking and home walking programmes, which can allow for monitoring (Hunter *et al* 2006). In this study activity monitoring was only utilised while patients were in hospital in order to compare the baseline physical activity levels of the patients in the control and experimental groups. Further research could possibly look at patterns of physical activity during hospitalisation and following discharge from hospital. Does NMES confine patients to bed? It could be that clinicians need to educate patients of the importance of physical

activity, and that it is not enough for patients just to use the NMES unit each day.

Future research could also look towards tightening the inclusion criteria for those recruited for the study. This study recruited patients admitted with an acute exacerbation of COPD however in order to target the more disabled patients selection could take into account severity of exacerbation and baseline levels of exercise tolerance, however this would prove very time consuming. It may be that a proportion of less disabled patients may benefit more from a voluntary training programme of quadriceps strengthening rather than NMES; a direct comparison of the two interventions would be valuable.

The current studies decline in strain gauge measurements following discharge from hospital may also provide scope for research into compliance with the NMES protocol. Levels of compliance could be monitored, some NMES units contain software to record how often the device has been worn, qualitative research could be conducted to identify barriers to compliance and since resources are always scarce this could aid recruitment towards those likely to comply. Some patients may also be less likely to participate in physical activity as they may feel that since they are using NMES that they do not need to, in this case educating the patient is particularly important. A crossover study may also give validity to study results if there were no time constraints.

Conclusion

In conclusion this study has shown that a 4-week NMES programme is feasible for patients suffering an exacerbation of COPD, and may have a role in maintaining physical capacity in patients hospitalised with an acute exacerbation. However these should be viewed as preliminary findings which would require confirmation by further studies incorporating larger sample sizes.

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Appendices

Appendix 1

THE BORG BREATHLESSNESS SCORE

0	NOTHING AT ALL
0.5	VERY, VERY SLIGHT
1.0	VERY SLIGHT
2.0	SLIGHT
3.0	MODERATE
4.0	SOMEWHAT SEVERE
5.0	SEVERE
6.0	
7.0	VERY SEVERE
8.0	
9.0	VERY, VERY SEVERE (ALMOST MAXIMAL)
10	MAXIMAL

(N.B. There is no ‘right’ or ‘wrong’ way with this scoring. It is just how you feel at the time. It is helpful for us to know how difficult you find each exercise).

PERCEIVED EXERTION

6

7 VERY, VERY LIGHT

8

9 VERY LIGHT

10

11 FAIRLY LIGHT

12

13 SOMEWHAT HARD

14

15 HARD

16

17 VERY HARD

18

19 VERY, VERY HARD

20

This scale is used to determine how hard you find the walking. There is no right or wrong response. Please take into account your breathing and how your muscles feel to give an overall score.

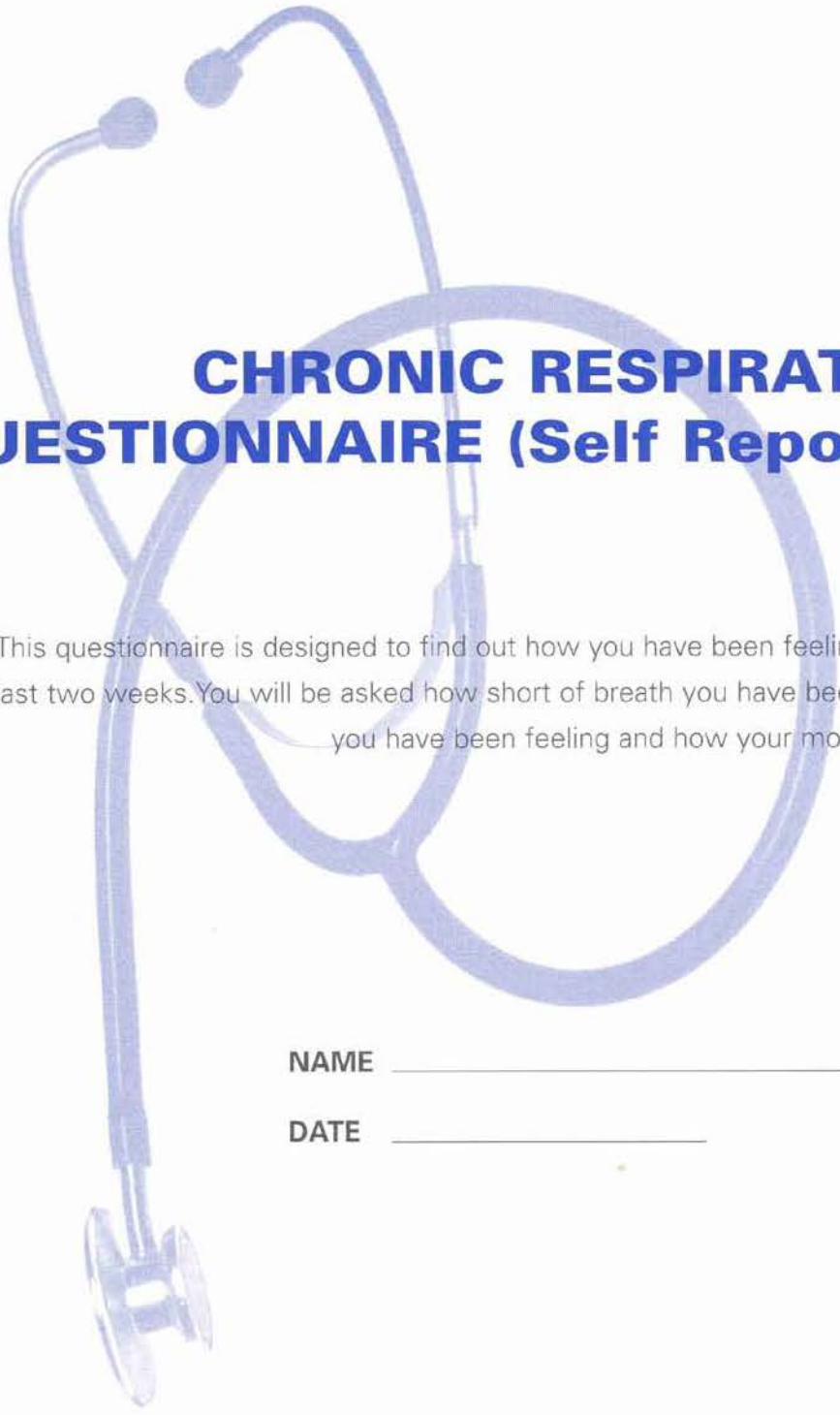
Appendix 2

MRC DYSPNOEA SCALE

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than people of the same age on the level ground because of breathlessness or has to stop for breath when walking at own pace
4	Stops for breath after walking about 100m or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when dressing or undressing

As appears in the NICE guideline on COPD

Adapted from Fletcher CM, Elmes PC, Fairbairn et al (1959) The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *British Medical Journal* 2:257-66



CHRONIC RESPIRATORY QUESTIONNAIRE (Self Reported)

This questionnaire is designed to find out how you have been feeling during the last two weeks. You will be asked how short of breath you have been, how tired you have been feeling and how your mood has been.

NAME _____

DATE _____

University Hospitals of Leicester NHS
NHS Trust

CHRONIC RESPIRATORY QUESTIONNAIRE (Self Reported)

We would like you to think of ways in which your shortness of breath limits your life. We are particularly interested in activities which you still do, but which are limited by your shortness of breath.

Listed below are some activities which can make people with lung problems feel short of breath.

If you have felt **short of breath** doing any of the **activities** listed below **during the last two weeks** then please tick each relevant activity. If you have **not** done the activity during the last two weeks or it does **not** make you short of breath then leave it blank.

THE ACTIVITIES ARE:

☐	1. BEING ANGRY OR UPSET
☐	2. HAVING A BATH OR SHOWER
☐	3. BENDING
☐	4. CARRYING - SUCH AS GROCERIES
☐	5. DRESSING
☐	6. EATING
☐	7. GOING FOR A WALK
☐	8. DOING YOUR HOUSEWORK
☐	9. HURRYING
☐	10. MAKING YOUR BED
☐	11. MOPPING OR SCRUBBING A FLOOR
☐	12. MOVING FURNITURE
☐	13. PLAYING WITH CHILDREN/GRANDCHILDREN
☐	14. PLAYING SPORTS
☐	15. REACHING OVER YOUR HEAD
☐	16. RUNNING - SUCH AS FOR A BUS
☐	17. SHOPPING
☐	18. WHILE TRYING TO SLEEP
☐	19. TALKING
☐	20. VACUUMING
☐	21. WALKING AROUND YOUR OWN HOME
☐	22. WALKING UPHILL
☐	23. WALKING UPSTAIRS
☐	24. WALKING WITH OTHERS ON LEVEL GROUND
☐	25. PREPARING MEALS

Please list **any other activities** that you have done during the last two weeks which have made you feel short of breath. These should be activities which you do frequently and which are important in your day-to-day life.

_____

_____

We would now like you to identify the **most <u>important</u> activities** in which you have been limited by your **shortness of breath** in the last **two weeks**.

Using the list you have made on the previous page, write down the **<u>five most important activities</u>** that have made you short of breath on the lines below. We would then like you to tell us **how short of breath** you have been while performing each activity by ticking the box which best describes how you feel.

HOW SHORT OF BREATH HAVE YOU BEEN DURING THE LAST TWO WEEKS WHILE PERFORMING THESE ACTIVITIES?

	Extremely short of breath	Very short of breath	Quite short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at all short of breath
1. _____	☐	☐	☐	☐	☐	☐	☐
2. _____	☐	☐	☐	☐	☐	☐	☐
3. _____	☐	☐	☐	☐	☐	☐	☐
4. _____	☐	☐	☐	☐	☐	☐	☐
5. _____	☐	☐	☐	☐	☐	☐	☐

PLEASE MAKE SURE YOU HAVE COMPLETED THE ABOVE TABLE BEFORE TURNING THE PAGE

Thank you

CHRONIC RESPIRATORY QUESTIONNAIRE (Self Reported)

6. In general, how much of the time during the last 2 weeks have you felt frustrated or impatient?

Please indicate how often during the last 2 weeks you have felt frustrated or impatient by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

7. How often during the past 2 weeks did you have a feeling of fear or panic when you had difficulty getting your breath?

Please indicate how often you had a feeling of fear or panic when you had difficulty getting your breath by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

8. What about fatigue? How tired have you felt over the last 2 weeks?

Please indicate how tired you have felt over the last 2 weeks by ticking one of the following options from the list below.

1. EXTREMELY TIRED ❑
2. VERY TIRED ❑
3. QUITE A BIT OF TIREDNESS ❑
4. MODERATELY TIRED ❑
5. SOMEWHAT TIRED ❑
6. A LITTLE TIRED ❑
7. NOT AT ALL TIRED ❑

9. How often during the last 2 weeks have you felt embarrassed by your coughing or heavy breathing?

Please indicate how much of the time you felt embarrassed by your coughing or heavy breathing by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

10. In the last 2 weeks, how much of the time did you feel very confident and sure that you could deal with your illness?

Please indicate how much of the time you felt very confident and sure that you could deal with your illness by ticking one of the following options from the list below.

1. NONE OF THE TIME ❑
2. A LITTLE OF THE TIME ❑
3. SOME OF THE TIME ❑
4. A GOOD BIT OF THE TIME ❑
5. MOST OF THE TIME ❑
6. ALMOST ALL OF THE TIME ❑
7. ALL OF THE TIME ❑

11. How much energy have you had in the last 2 weeks?

Please indicate how much energy you have had by ticking one of the following options from the list below.

1. NO ENERGY AT ALL ❑
2. A LITTLE ENERGY ❑
3. SOME ENERGY ❑
4. MODERATELY ENERGETIC ❑
5. QUITE A BIT OF ENERGY ❑
6. VERY ENERGETIC ❑
7. FULL OF ENERGY ❑

CHRONIC RESPIRATORY QUESTIONNAIRE (Self Reported)

12. In general, how much of the time did you feel upset, worried or depressed during the past 2 weeks?

Please indicate how much of the time you felt upset, worried or depressed during the past 2 weeks by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

13. How often during the last 2 weeks did you feel you had complete control of your breathing problems?

Please indicate how often you felt you had complete control of your breathing problems by ticking one of the following options from the list below.

1. NONE OF THE TIME ❑
2. A LITTLE OF THE TIME ❑
3. SOME OF THE TIME ❑
4. A GOOD BIT OF THE TIME ❑
5. MOST OF THE TIME ❑
6. ALMOST ALL OF THE TIME ❑
7. ALL OF THE TIME ❑

14. How much of the time during the last 2 weeks did you feel relaxed and free of tension?

Please indicate how much of the time you felt relaxed and free of tension by ticking one of the following options from the list below.

1. NONE OF THE TIME ❑
2. A LITTLE OF THE TIME ❑
3. SOME OF THE TIME ❑
4. A GOOD BIT OF THE TIME ❑
5. MOST OF THE TIME ❑
6. ALMOST ALL OF THE TIME ❑
7. ALL OF THE TIME ❑

15. How often during the last 2 weeks have you felt low in energy?

Please indicate how often during the last 2 weeks you have felt low in energy by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

16. In general, how often during the last 2 weeks have you felt discouraged or down in the dumps?

Please indicate how often during the last 2 weeks you felt discouraged or down in the dumps by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

17. How often during the last 2 weeks have you felt worn out or sluggish?

Please indicate how much of the time you felt worn out or sluggish by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

CHRONIC RESPIRATORY QUESTIONNAIRE (Self Reported)

18. How happy, satisfied or pleased have you been with your personal life during the last 2 weeks?

Please indicate how happy, satisfied or pleased you have been by ticking one of the following options from the list below.

1. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME ❑
2. GENERALLY DISSATISFIED, UNHAPPY ❑
3. SOMEWHAT DISSATISFIED, UNHAPPY ❑
4. GENERALLY SATISFIED, PLEASED ❑
5. HAPPY MOST OF THE TIME ❑
6. VERY HAPPY MOST OF THE TIME ❑
7. EXTREMELY HAPPY, COULD NOT HAVE BEEN MORE SATISFIED OR PLEASED ❑

19. How often during the last 2 weeks did you feel upset or scared when you had difficulty getting your breath?

Please indicate how often during the past 2 weeks you felt upset or scared when you had difficulty getting your breath by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

20. In general how often during the last 2 weeks have you felt restless, tense or uptight?

Please indicate how often you have felt restless, tense or uptight by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

Thank you very much for taking the time to complete this questionnaire.

HAD Scale

Your nurse is aware that emotions play an important part in your illness and treatment. If your nurse knows about these feelings he will be able to help you more.

This questionnaire is designed to help your nurse to know how you feel. Read each item and place a firm tick in the box opposite the reply, which comes closest to how you have been feeling in the past week.

Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought-out response.

Tick one box only in each section

1 I feel tense or wound up:
- Most of the time ☐
- A lot of the time ☐
- Time to time, occasionally ☐
- Not at all ☐

2 I still enjoy the things I used to enjoy:
- Definitely as much ☐
- Not quite so much ☐
- Only a little ☐
- Hardly at all ☐

3 I get a sort of frightened feeling as if something awful is about to happen:
- Very definitely and quite badly ☐
- Yes, but not too badly ☐
- A little, but it doesn't worry me ☐
- Not at all ☐

4 I can laugh and see the funny side of things:
- As much as I always could ☐
- Not quite so much now ☐
- Definitely not so much now ☐
- Not at all ☐

5 Worrying thoughts go through my mind:
- A great deal of the time ☐
- A lot of the time ☐
- From time to time bur not too often ☐
- Only occasionally ☐

6 I feel cheerful
- Not at all ☐
- Not often ☐
- Sometimes ☐
- Most of the time ☐

7 I can sit at ease and feel relaxed:
- Definitely ☐
- Usually ☐
- Not often ☐
- Not at all ☐

8 I feel as if I am slowed down:
- Nearly all the time ☐
- Very often ☐
- Sometimes ☐
- Not at all ☐

9 I get a sort of frightened feeling like "butterflies" in the stomach:
- Not at all ☐
- Occasionally ☐
- Quite often ☐
- Very often ☐

10 I have lost interest in my appearance:
- Definitely ☐
- I don't take so much care as I should ☐
- I may not take quite as much care ☐
- I take just as much care as ever ☐

11 I feel restless as if I have to be on the move:
- Very much indeed ☐
- Quite a lot ☐
- Not very much ☐
- Not at all ☐

12 I look forward with enjoyment to things:
- As much as I ever did ☐
- Rather less than I used to ☐
- Definitely less than I used to ☐
- Hardly at all ☐

13 I get sudden feelings of panic:
- Very often indeed ☐
- Quite often ☐
- Not very often ☐
- Not at all ☐

14 I can enjoy a good book or radio or TV programme:
- Often ☐
- Sometimes ☐
- Not often ☐
- Very seldom ☐

Appendix 4.

How To Put The Activity Monitor Device On Yourself

What Does The Activity Monitor Device Measure?

The Activity Monitor Device has sensors that detect movement.
From this data the Activity Monitor Device calculates energy expenditure as well as amount of time active, lying down and sleeping.

How To Put The Activity Monitor Device On Yourself

The Activity Monitor Device is to be worn on the back above the elbow of your right arm. Position Activity Monitor with the timestamp button above the battery cover and slide the device along the back of the arm mid way between the elbow and the shoulder. Adjust the strap so that it fits onto your arm comfortable and secure with the Velcro. Please take care not to adjust the strap too tightly, if your arm begins to tingle, lose feeling or is uncomfortable loosen the strap.
Once you have put the monitor on the device will switch itself on and will give off a tone (do-de-do-deet) and then will vibrate for two seconds.
To take off the arm simply loosen the strap and slide down the arm and take off the device once off will give off a tone (de-de-deet).

When To Wear It And When To Take It Off

You can wear the monitor while you are up and about as well as while you are lying or sleeping. However you should always remove while you are washing so not to get the device wet. You must also remove while you are using the Muscle Stimulators so there is no electrical interference. If there is any skin irritation caused by wearing the device please remove it, only replace you are comfortable to put the monitor back on.

How Long Can It Be Used For?

The battery life of the Activity Monitor Device is on average 14 days and the memory capacity for the device is 10 days and 21 hours. The data can be transferred on to computer before filled and the batteries can be easily replaced.

If you have any questions please phone on Ext. 3181

Appendix 5.

Appendix 6

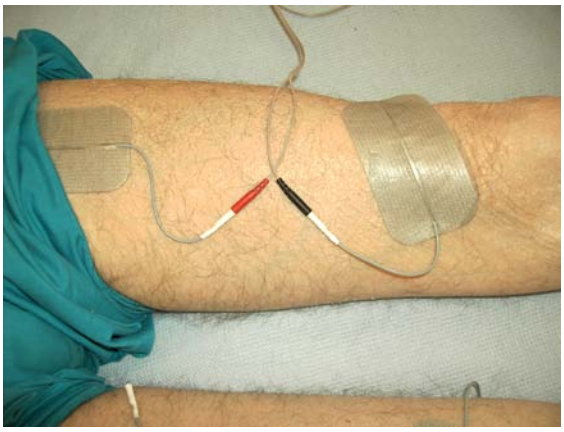
How to Put the Muscle Stimulator Device on Yourself.

1. Sit down in a comfortable position with your legs supported and stretched out in front of you.

2. Then expose the top part of you leg to reveal the Quadriceps muscle (this is the muscle that runs on the front of your thigh between your hip and your knee).

3. Gently un-peal your stickers from their plastic backing one at a time and place on the legs as the picture below shows: (2 just above the knee at an angle and the other 2 at the tops of the thighs in the middle).

4. Then attach the leads from the device to the leads attached to the sticky pads. The red connector goes into the pad at the top of the leg and the black goes into the pad just above the knee.

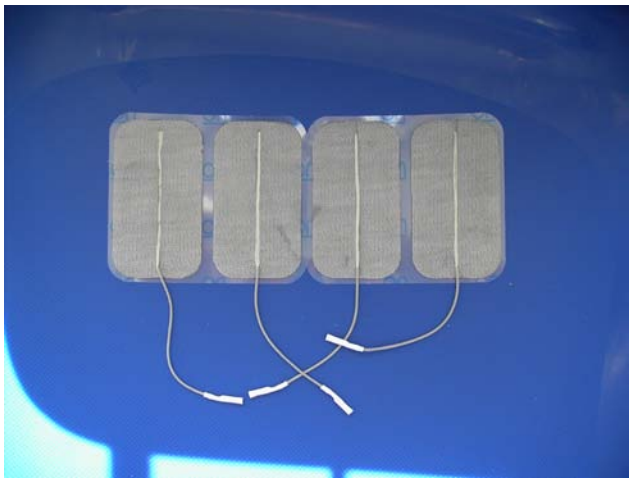


5. Turn the device on by pressing the red button. The programme you are on is automatically switched on.

6. Gradually turn up the device on both sides by pressing the up buttons (see below). Keep turning the device up until you start to feel the tingling and gradually increase this as you can tolerate.

7. The device automatically counts 20 minutes for you so when it has finished turn the device off using the red button again and unplug the connectors from the sticky pads.

8. Gently peel the sticky pads off your legs and place back onto the protective plastic backing, ready for next time.



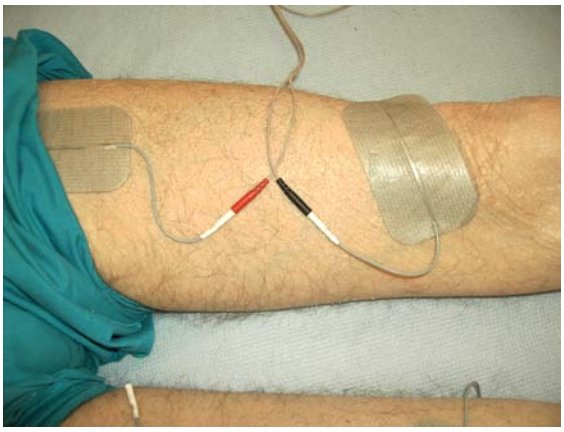
How to Put the Muscle Stimulator Device on Yourself.

1. Sit down in a comfortable position with your legs supported and stretched out in front of you.

2. Then expose the top part of you leg to reveal the Quadriceps muscle (this is the muscle that runs on the front of your thigh between your hip and your knee).

3. Gently un-peel your stickers from their plastic backing one at a time and place on the legs as the picture below shows: (2 just above the knee at an angle and the other 2 at the tops of the thighs in the middle).

4. Then attach the leads from the device to the leads attached to the sticky pads. The red connector goes into the pad at the top of the leg and the black goes into the pad just above the knee.

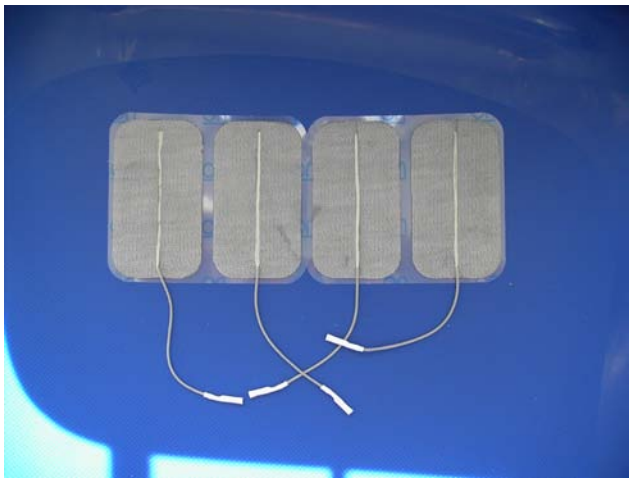


5. Turn the device on by pressing the red button. The programme you are on is automatically switched on.

6. Gradually turn up the device on both sides by pressing the up buttons (see below). Keep turning the device up until you start to feel the sensation or visibly see a muscle contraction, and gradually increase this as you can tolerate.

7. The device automatically counts 20 minutes for you so when it has finished unplug the connectors from the sticky pads.

8. Gently peel the sticky pads off your legs and place back onto the protective plastic backing, ready for next time.



Appendix 7.

Chronic Respiratory

Questionnaire
(Self Reported) - Follow up

Name:
Date:

You have previously completed a questionnaire telling us about how you have been feeling and how your lung disease has affected your life. This is a follow-up questionnairedesigned to find out how you have been getting on since then.

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Chronic Respiratory Questionnaire

We asked you previously to identify the **five most important activities** in your life which were limited by **shortness of breath**. Listed below is the list of activities which you selected. Please could you tell us **how short of breath** you have been in the last two weeks while performing each activity by ticking the box which best describes how you feel.

How short of breath have you been during the last two weeks while performing these activities?

Extremely Short of Breath
Very Short of Breath
Quite Short of Breath
Moderate Shortness of Breath
Some Shortness of Breath
A little Shortness of Breath
Not at all short of Breath

1.
2.
3.
4.
5.

Please make sure you have completed the above table before continuing onto the multiple choice questions on the next page.....

The activities are: Please one box per activity

Chronic Respiratory Questionnaire

6. In general, how much of the time during the last 2 weeks have you felt frustrated or impatient?

Please indicate how often during the last 2 weeks you have felt frustrated or impatient by ticking one of the following options from the list below.

1 All of the time _
2 Most of the time _
3 A good bit of the time _
4 Some of the time _
5 A little of the time _
6 Hardly any of the time _
7 None of the time _

7. How often during the past 2 weeks did you have a feeling of fear or panic when you had difficulty getting your breath?

Please indicate how often you had a feeling of fear or panic when you had difficulty getting your breath by ticking one of the following options from the list below.

1 All of the time _
2 Most of the time _
3 A good bit of the time _
4 Some of the time _
5 A little of the time _
6 Hardly any of the time _
7 None of the time _

8. What about fatigue? How tired have you felt over the last 2 weeks?

Please indicate how tired you have felt over the last 2 weeks by ticking one of the following options from the list below.

1 Extremely tired _
2 Very tired _
3 Quite a bit of tiredness _
4 Moderately tired _
5 Somewhat tired _
6 A little tired _
7 Not at all tired _

9. How often during the last 2 weeks have you felt embarrassed by your coughing or heavy breathing?

Please indicate how much of the time you felt embarrassed by your coughing or heavy breathing by ticking one of the following options from the list below.

1 All of the time _
2 Most of the time _

3 A good bit of the time _
4 Some of the time _
5 A little of the time _
6 Hardly any of the time _
7 None of the time _

10. In the last 2 weeks, how much of the time did you feel very confident and sure that you could deal with your illness?

Please indicate how much of the time you felt very confident and sure that you could deal with your illness by ticking one of the following options from the list below.

1 None of the time _
2 A little of the time _
3 Some of the time _
4 A good bit of the time _
5 Most of the time _
6 Almost all of the time _
7 All of the time _

11. How much energy have you had in the last 2 weeks?

Please indicate how much energy you have had by ticking one of the following options from the list below.

1 No energy at all _
2 A little energy _
3 Some energy _
4 Moderately energetic _
5 Quite a bit of energy _
6 Very energetic _
7 Full of energy _

12. In general, how much of the time did you feel upset, worried or depressed during the past 2 weeks?

Please indicate how much of the time you felt upset, worried or depressed during the past 2 weeks by ticking one of the following options from the list below.

1 All of the time _
2 Most of the time _
3 A good bit of the time _
4 Some of the time _
5 A little of the time _
6 Hardly any of the time _
7 None of the time _

13. How often during the last 2 weeks did you feel you had complete control of your breathing problems?

Please indicate how often you felt you had complete control of your breathing problems by ticking one the following options from the list below.

1 None of the time _
2 A little of the time _
3 Some of the time _
4 A good bit of the time _
5 Most of the time _
6 Almost all of the time _
7 All of the time _

14. How much of the time during the last 2 weeks did you

feel relaxed and free of tension?
Please indicate how much of the time you felt relaxed and free of tension by ticking one of the following options from the list below.
1 None of the time _
2 A little of the time _
3 Some of the time _
4 A good bit of the time _
5 Most of the time _
6 Almost all of the time _
7 All of the time _

15. How often during the last 2 weeks have you felt low in energy?
Please indicate how often during the last 2 weeks you have felt low in energy by ticking one of the following options from the list below.
1 All of the time _
2 Most of the time _
3 A good bit of the time _
4 Some of the time _
5 A little of the time _
6 Hardly any of the time _
7 None of the time _
16. In general, how often during the last 2 weeks have you felt discouraged or down in the dumps?
Please indicate how often during the last 2 weeks you felt discouraged or down in the dumps by ticking one of the following options from the list below.
1 All of the time _
2 Most of the time _
3 A good bit of the time _
4 Some of the time _
5 A little of the time _
6 Hardly any of the time _
7 None of the time _
17. How often during the last 2 weeks have you felt worn out or sluggish?
Please indicate how much of the time you felt worn out or sluggish by ticking one of the following options from the list below.
1 All of the time _
2 Most of the time _
3 A good bit of the time _
4 Some of the time _
5 A little of the time _
6 Hardly any of the time _
7 None of the time _

18. How happy, satisfied or pleased have you been with your personal life during the last 2 weeks?
Please indicate how happy, satisfied or pleased you have been by ticking one of the following options from the list below.

1 Very dissatisfied, unhappy most of the time _
2 Generally dissatisfied, unhappy _
3 Somewhat dissatisfied, unhappy _
4 Generally satisfied, pleased _
5 Happy most of the time _
6 Very happy most of the time _
7 Extremely happy, could not have been
more satisfied or pleased _

19. How often during the last 2 weeks did you feel upset or scared when you had difficulty getting your breath?

Please indicate how often during the last 2 weeks you felt upset or scared when you had difficulty getting your breath by ticking one of the following options from the list below.

1 All of the time _
2 Most of the time _
3 A good bit of the time _
4 Some of the time _
5 A little of the time _
6 Hardly any of the time _
7 None of the time _

20. In general, how often during the last 2 weeks have you felt restless, tense or uptight?

Please indicate how often you have felt restless, tense or uptight by ticking one of the following options from the list below.

1 All of the time _
2 Most of the time _
3 A good bit of the time _
4 Some of the time _
5 A little of the time _
6 Hardly any of the time _
7 None of the time _

Thank you very much for taking the time to complete this questionnaire.

Appendix 8.

CONSENT FORM (Version 3, 19/06/07)

Identification Number for this study: **07/Q2501/5**

Is neuromuscular electrical stimulation effective in maintaining physical capacity during an exacerbation of COPD?

Please initial box

1. I confirm that I have read and understand the information sheet dated 19/06/07 version 3 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐
5. I agree for my consultant to be informed of my participation. ☐

_____	_____	_____
Name of Patient	**Date**	
Signature		

_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 9.

Date

Dr …….
Address

Dear Dr

Study title**: Neuromuscular electrical stimulation is effective in maintaining physical capacity during an exacerbation of COPD.**

A study has been designed to establish whether neuromuscular electrical stimulation is an effective adjuvant rehabilitative therapy, suitable during an exacerbation of COPD.
On Admission to hospital patients quadriceps strength, and incremental shuttle walk distances will be tested. They will be asked to wear activity monitors. The treatment group will receive quadriceps muscle stimulation for 30 minutes each day on each leg for a total of 6 weeks, patients will be asked to administer this on discharge from hospital. The control group will receive stimulation at sub-therepeutic levels. 6 weeks after commencing the stimulation patients will be recalled and their quads strength and shuttle walk distances will once again be tested.

We would be grateful if we could obtain your permission to approach the patients under your care.

If you require any further information please do not hesitate to contact me on (0116) 250 2535.

Yours sincerely

Sally Singh PhD
Head of Pulmonary & Cardiac Rehabilitation
Jennie Bradshaw
Research student

Appendix 10.

PATIENT INFORMATION SHEET
(Version 3 19/06/07)

1. Study title:

Neuromuscular electrical stimulation is effective in maintaining physical capacity during an exacerbation of COPD.

You are being invited to take part in a research study being conducted by the pulmonary rehabilitation team in conjunction with Coventry University. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

2. What is the purpose of the study?

There is evidence to suggest that muscle stimulation is a beneficial component of rehabilitation for sufferers of Chronic Obstructive Pulmonary Disease (COPD). However this has only been investigated in patients whose disease is stable. We also know that during hospitalisation there is a decline in the overall function of your leg muscles. We hope to prevent this decline by applying a device that will stimulate your muscle.

3. Why have I been chosen?

You have been identified as suitable to participate in this study because you have been admitted to hospital with a worsening of your COPD.

4. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

5. What will happen to me if I take part?

Once you have agreed to take part in the research you will be visited by a member of the research team. You will have an opportunity to ask any questions you may have, and you will be asked to sign a consent form to confirm your participation. With your permission we will also contact your consultant to check that they are agreeable to your participation. Sometimes we don't know which way of treating patients is best. To find out we need to make comparisons between the different treatments. We put people into groups and give each group a different treatment; the result are compared to see if one is better. To try to

make sure the groups are the same to start with, each participant is put into a group by chance (randomly). The results are then compared. There is a one in two chance of getting the treatment. The trial is also 'blind'. In a 'blind trial' you will not know which treatment group you are in.

6. What do I have to do?

The research will consist firstly of a measure of the strength of your thigh muscle, this is entirely painless, we will also ask that you complete a simple exercise test, and wear an activity monitor. You will then be randomised to receive either the active or placebo treatment. You will than be introduced to the muscle stimulation unit, we would ask that you place the pads on each thigh for thirty minutes a day for the four week duration of the study, you will be taught how to use the unit prior to your discharge from hospital. This treatment would continue at home regardless of the group you were allocated to. The device is very similar to a 'slendertone' type of equipment. Athletes often use the Equipment when they are injured to restore muscle function. The device produces a tingling sensation, which is not uncomfortable When you are ready to be discharged we will repeat the muscle strength test, and the exercise test. Four weeks after beginning the study you will be invited to return to the Glenfield Hospital to repeat the tests and again after 6 months. Travel expenses will be paid. At the beginning and end of the study you will also be requested to complete a simple questionnaire regarding your current state of health.

7. What are the possible disadvantages and risks of taking part?

There are no foreseeable side effects of taking part, however completing the muscle stimulation for the Four -week period may cause some inconvenience.

8. What are the possible benefits of taking part?

We hope that the research will inform further rehabilitative strategies for patients with COPD who suffer an exacerbation, and possibly prevent future readmission to hospital.

10. What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangement. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms would be available to you. Advice can also be sought from the Patient Advice and Liaison Service (PALS).

11. Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it. Participants will not be identified in any subsequent written material, for example, pseudonyms will be used to refer to participants' names. Any information that you give will be used for research purposes only. Results will be reported in such a way that completely preserves confidentiality.

12. What will happen to the results of the research study?

The results of the study will be disseminated in a thesis towards a masters degree, results may also be reported in professional publications and presentations made at relevant conferences. Results will be reported in such a way that preserves confidentiality. All participants will be given an opportunity to receive a summary of the results if interested. You will not be automatically sent one in order to keep financial costs to a minimum, but will be given an opportunity to request one at your 4 week follow up.

13. Who is organising and funding the research?

This study is being funded by the Pulmonary Rehabilitation Research Group and the Pulmonary and Rehabilitation team will be organising the study and recruiting participants.

14. Who has reviewed the study?

All research that involves NHS patients or staff, information fro NHS medical records or uses NHS premises or facilities must be approved by an NHS research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information of which to make an informed decision.

15. Contact for further information

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the principal researcher (Sally Singh Tel:0116 2502535)

Contact for further information:

Sally Singh, head of cardiac and pulmonary rehabilitation

Glenfield Hospital

Groby Road

Leicester

LE3 9QP

email s.singh@uhl-tr.nhs.uk

Thank you for reading this

Sally Singh

Consultant Clinical Scientist

Appendix 11

Ethical approval

This form has been removed for copyright reasons